EXHIBIT 37

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Control Nos.:	**90/ 007,542** **90/ 007,859**		Group Art Unit:	3991
Confirmation Nos.:	7585 ('542) 6447 ('859)		Examiner:	P. Ponnaluri
Filed:	13 May 2005 23 December 2005	('542) ('859)		
Patent Owner:	Genentech, Inc. and City of Hope			

For: Merged Reexaminations of U.S. Patent No. 6,331,415 (Cabilly et al.)

Mail Stop **Ex Parte Reexam**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

Further to the Notice of Appeal under 37 C.F.R. § 41.31 filed in this merged reexamination proceeding on 22 August 2008, Owners file this appeal brief in compliance with § 41.37. On 17 October 2008, the Office granted a request to extend the time for filing a brief to 10 December 2008. Accordingly, this brief is timely filed.

Owners request that the Director debit the fee for filing an appeal brief, **$540** (§ 41.20(b)(2)), as well as any other fees required to make this or any other paper submitted in support of this appeal timely or proper, from our **Deposit Account No. 18-1260**.

Sections (1) to (7) below correspond to the requirements of § 41.37(c)(1)(i)-(vii), respectively. The sections required under § 41.37(c)(1)(viii)-(x) appear as appendices to this brief.

Table of Contents

TABLE OF AUTHORITIES

CASES

STATUTES

MISCELLANEOUS

(1) Real Party in Interest

The real parties in interest are Genentech, Inc., a corporation organized under the laws of the State of Delaware, and City of Hope, a corporation organized under the laws of the State of California.

(2) Related Appeals, Interferences, and Judicial Proceedings

No prior or pending appeals related to this proceeding within the meaning of 37 C.F.R. § 41.37(c)(1)(ii) are known to appellants or counsel.

The patent under reexamination, U.S. Patent No. 6,331,415 [App. B49-72] ("the '415 patent"), has been involved in the proceedings noted below. The listed decisions from those proceedings appear in the Related Proceedings Appendix at the page numbers noted in brackets.

- Cabilly v. Boss, Interference No. 102,572, involving the application on which the patent under reexamination was granted, serial no. 07/205,419, and U.S. Patent No. 4,816,397 to Boss et al. After entry of an initial adverse judgment, priority was eventually awarded to Cabilly et al. following judgment in an action under 35 U.S.C. § 146.
  - Final Decision, 55 U.S.P.Q.2d 1238 (Bd. Pat. App. & Interf., 13 August 1988) [App. C1-58]
  - Final Order after District Court Judgment, 60 U.S.P.Q.2d 1752 (Bd. Pat. App. & Interf., 26 July 2001) [App. C59-73]
- Genentech, Inc. v. Celltech Therapeutics, Ltd., Civil Action No. C98-3926 MMC (WDB) (N.D. Cal.) (§ 146 action seeking review of judgment in Interference No. 102,572)
  - Judgment (16 March 2001) [App. C74-77]
- MedImmune, Inc. v. Genentech, Inc., Civil Action No. CV03-02567 MRP (CTx) (C.D. Cal.) (settled)
  - Amended Memorandum of Decision Re: Defendant Celltech's Motion for Judgment on the Pleadings and Defendant Genentech's Motion for Summary Judgment (C.D. Cal., 14 January 2004) [App. C78-103]
  - 427 F.3d 958, 76 U.S.P.Q.2d 1914 (Fed. Cir. 2005) [App. C104-120]
  - 549 U.S. 118, 81 U.S.P.Q.2d 1225 (2007) [App. C121-142]
  - Claim Construction Order (C.D. Cal., 16 August 2007) [App. C143-169]
- Centocor, Inc. v. Genentech, Inc., Civil Action No. CV08-03573 PA (AGRx) (W.D. Cal.) (pending)

Applications related to the patent under reexamination have been involved in the proceedings noted below. The listed decision appears in the Related Proceedings Appendix at the page numbers noted in brackets.

- Cabilly v. Glaxo Wellcome Inc., Interference No. 104,532, involving application serial no. 08/909,611, which claimed priority to the patent under reexamination (terminated)
  - Order Denying Glaxo Wellcome Miscellaneous Motion 1, 56 U.S.P.Q.2d 1983, Bd. Pat. App. & Interf., 26 October 2000) [App. C170-172]
  - Decision on Priority and Other Motions and Final Judgment (Bd. Pat. App. & Interf., 4 September 2002) [App. C173-230]
- Cabilly v. Boss, Interference No. 105,531, involving application serial no. 08/422,187, which claims priority to the patent under reexamination (pending)
  - Memorandum Opinion and Order (Decision on Cabilly Motion 1 – estoppel) (Bd. Pat. App. & Interf., 4 June 2008) [App. C231-263]
  - Memorandum Opinion and Order (Decision on Cabilly Motion 2 – patentability) (Bd. Pat. App & Interf., 8 December 2008) [App. C264-284]
  - Memorandum Opinion and Order (Decision on Cabilly Motion 5 – priority) (Bd. Pat. App & Interf., 8 December 2008) [App. C285-312]
  - Judgment (Bd. Pat. App & Interf., 8 December 2008) [App. C313-316].

(3) Status of Claims

Claims 1-36 were granted in the '415 patent and have not been amended in this proceeding.

Claims 1-36 stand finally rejected and are involved in this appeal.

(4) Status of Amendments

A reply under 37 C.F.R. § 1.116 was filed on June 6, 2008, together with two declarations under § 1.132. The reply did not include amendments to the claims. In an advisory action mailed on July 19, 2008, the Examiner indicated that the reply and declarations would be entered.

(5) Summary of Claimed Subject Matter

The invention relates generally to methods for recombinantly producing immunoglobulin molecules or immunologically functional immunoglobulin fragments (collectively "immunoglobulin multimers" or "multimeric immunoglobulin structures").[1] The methods of the invention require the immunoglobulin multimer to be made from immunoglobulin heavy and light chains produced in a single recombinantly transformed host cell. In particular, the claims require transforming a single host cell with DNA sequences encoding the heavy chain and light chain, and independently expressing both sequences such that the heavy chain and light chain polypeptides are both produced as separate molecules in the same host cell.

Claims 1-18 of the '415 patent were copied (with minor variations appropriate to the disclosure of the application filed by Cabilly et al.) from U.S. Patent No. 4,816,397 to Boss et al. The Office declared an interference (Interference No. 102,572), designating claim 1 of the '415 patent as the Count. Priority of invention was awarded to Cabilly following an action under 35 U.S.C. § 146. See section (2) above and the Related Proceedings appendix to this brief.

The specific text of various limitations of the independent claims finds support at least in the passages of the '415 patent and the claims of the original application (i.e., serial no. 07/205,419 ("the '419 application")) as indicated below.

1.	A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell, comprising the steps of:	Col. 3, line 42 - col. 4, line 5; col. 4, line 51 - col. 5, line 39; col. 6, lines 3-11; col. 7, lines 35-39, 47-59; col. 12, lines 17-22, 26-30, 50-56; col. 16, lines 6-10; col. 23, lines 5-10.

[1] Immunoglobulin molecules and immunologically functional immunoglobulin fragments are "multimeric" protein complexes made up of multiple discrete immunoglobulin polypeptides. The multimeric immunoglobulin complex is formed through disulfide bonds and non-covalent associations between the discrete polypeptides. See '415 patent, col. 3. lines 16-40.

	(i) transforming said single host cell with a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a second DNA sequence encoding at least the variable domain of the immunoglobulin light chain, and	Col. 3, lines 42-45; col. 8, lines 26-32; col. 12, lines 17-30; col. 23, lines 5-10.
	(ii) independently expressing said first DNA sequence and said second DNA sequence so that said immunoglobulin heavy and light chains are produced as separate molecules in said transformed single host cell.	Col. 4, lines 24-29; col. 12, lines 17-22, 31-33, 50-56; col. 23, lines 16-33; col. 24, line 18.
15.	A vector comprising a first DNA sequence encoding at least a variable domain of an immunoglobulin heavy chain and a second DNA sequence encoding at least a variable domain of an immunoglobulin light chain wherein said first DNA sequence and said second DNA sequence are located in said vector at different insertion sites.	Col. 12, lines 9-22.
18.	A transformed host cell comprising at least two vectors, at least one of said vectors comprising a DNA sequence encoding at least a variable domain of an immunoglobulin heavy chain and at least another one of said vectors comprising a DNA sequence encoding at least the variable domain of an immunoglobulin light chain.	Col. 12, lines 23-27.
21.	A method comprising	Col. 3, lines 42-50; col. 4, lines 33-37; col. 6, lines 3-4; col. 14, lines 45-50.
	a) preparing a DNA sequence consisting essentially of DNA encoding an immunoglobulin consisting of an immunoglobulin heavy chain and light chain or Fab region, said immunoglobulin having specificity for a particular known antigen;	
	b) inserting the DNA sequence of step a) into a replicable expression vector operably linked to a suitable promoter;	Col. 8, lines 3-6, 16-25; col. 8, line 57 - col. 10, line 18.

c)	transforming a prokaryotic or eukaryotic microbial host cell culture with the vector of step b);	Col. 8, lines 33-36, 41-43.
d)	culturing the host cell; and	Col. 12, lines 31-32.
e)	recovering the immunoglobulin from the host cell culture, said immunoglobulin being capable of binding to a known antigen.	Col. 12, lines 36-39.

33. A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell, comprising: independently expressing a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a second DNA sequence encoding at least the variable domain of the immunoglobulin light chain so that said immunoglobulin heavy and light chains are produced as separate molecules in said single host cell transformed with said first and second DNA sequences.	Col. 4, line 51 - col. 5, line 39; col. 7, lines 35-39, 47-59; col. 12, lines 17-22, 27-30, 50-56; col. 16, lines 5-10; col. 23, lines 5-10.

(6) Grounds of Rejection to be Reviewed on Appeal

Claims 1-36 have been rejected under the nonstatutory doctrine of obviousness-type double patenting over claims 1-7 of U.S. Patent No. 4,816,567, [App. B49-72], ("the '567 patent") in view of the following references, as indicated at page 10 of the final Office action, [App. B1588-1637]:

- U.S. Patent No. 4,399,216 ("Axel"), [App. B73-100]
- Rice, D.A., et al. (1982) Proc. Nat'l Acad. Sci. USA 79: 7862-65 ("Rice"), [App. B101-104]
- EP 0 044 722 ("Kaplan"), [App. B105-122]
- U.S. Patent No. 4,511,502 ("Builder"), [App. B174-196]
- Accolla, R.S. et al. (1980) Proc. Nat'l Acad. Sci. USA 77: 563-66 ("Accolla"), [App. B170-173]
- WO 82/ 03088 ("Dallas"), [App. B137-151]
- Deacon, N.J., et al. (1976) Biochem. Soc. Trans. 4: 818-20 ("Deacon"), [App. B160-162]
- Valle, G., et al. (1981) Nature 291: 338-40 ("Valle 1981"), [App. B163-165]
- Ochi, A., et al. (1983) Nature 302: 340-42 ("Ochi"), [App. B152-154] alone, or further in view of U.S. Patent No. 5,840,545 ("Moore"), [App. B123-136]

(7) Argument

The Board should reverse the Examiner's rejection of the claims of the second Cabilly patent (the '415 patent) for obviousness-type double patenting over the claims of the first Cabilly patent (the '567 patent). Owners provided extensive evidence showing, inter alia, that the Examiner made serious errors by failing to properly identify and appreciate the important differences between the two patented inventions, and distorting both the teachings of the prior art and the expectations of a person of ordinary skill in the art in April 1983. The evidence instead demonstrates that: (i) the prior art does not disclose or suggest all of the limitations of the '415 patented invention, (ii) from the starting point of the '567 claimed invention, the prior art and general knowledge in the field would have led a person of ordinary skill away from (rather than toward) the '415 claimed approach of producing an immunoglobulin multimer in April 1983, (iii) a person of ordinary skill would not have had a reasonable basis for believing that the '415 claimed approach of making a complex multimeric immunoglobulin structure could have been predictably achieved based on the '567 claims and in view of the cited references, and (iv) there are powerful secondary indicia of non-obviousness, particularly substantial evidence of industry acquiescence and commercial success attributable solely to the '415 patented invention.

(a) The '415 Invention Was Made a Quarter Century Ago During the Infancy of the Biotechnology Industry

Obviousness must be assessed using the perspective of a person of ordinary skill in the art at the time of the invention. The effective filing date of the invention at issue is April 7, 1983. Conventional thinking in the field of the invention then – a quarter century ago – bears no resemblance to today. Accurately understanding the state of the art at that time, however, is of critical importance in this case.

In April 1983, scientists knew genetic engineering had tremendous potential, but had only begun to scratch the surface of the understandings necessary to realize that potential. Declaration of Dr. Timothy John Roy Harris, [App. B549-584], ("Harris II") ¶ 13. Early scientific breakthroughs showed that foreign DNA could be stably incorporated into a host cell, and, under the right conditions, expressed in that cell. Two applications of this discovery

enabled scientists to visualize the possibility of using "genetically engineered" cells to produce single desired polypeptides in feasible quantities.

First, scientists genetically "transformed" host cells by introducing "marker" genes into the cells. When expressed in a cell, a "marker" gene confers new properties onto the cell that enable a scientist to distinguish these genetically transformed cells from non-transformed cells. For example, scientists could introduce a gene into a cell that would enable it to survive in the presence of a chemical compound (a "selection agent") that killed untransformed cells. This advance not only enabled scientists to find the cells that had successfully incorporated and expressed the foreign gene, it also allowed them to apply "selective" evolutionary pressure on the cells. In other words, by allowing the cells to replicate in the presence of the selection agent, uniform cell cultures containing only "successfully" transformed host cells could be produced.

Second, scientists introduced other DNA sequences into the cell, in addition to the "marker" gene, that directed the cell to produce a single desired polypeptide (i.e., a polypeptide the scientist wanted to recover from the cell). By culturing the genetically transformed cells in the presence of the selection agent, cell cultures containing many copies of identically transformed host cells could be produced, and significant quantities of a desired polypeptide could be recovered from those cells.

However, in April 1983, the biological mechanisms that controlled expression of foreign DNA and assembly of proteins were not well understood. This lack of understanding was especially true for eukaryotic genes, which were known to be far more complex than prokaryotic genes. As Dr. Harris, one of Owners' experts in this case, explained in his 1983 review paper, "it is clear that not all the rules governing the expression of cloned genes have been elaborated and those rules that do exist are still largely empirical." Harris, Genetic Eng. 4:127-85, 129 (1983), [App. B466-525]; see also Second Declaration of Dr. Steven L. McKnight, [App. B375-388], ("McKnight II") ¶ 6. As a consequence, scientists working in this field at the time made conservative predictions about what could be achieved, and only by analogy to what had been previously achieved.

This conservative mentality was reflected in the choices that scientists made in April 1983 as to the types of proteins to produce and by how they approached production of these

proteins. For example, before April 1983, scientists chose almost exclusively to produce "monomeric" proteins (i.e., proteins consisting of a single polypeptide chain). Harris II ¶¶ 13-14; McKnight II ¶¶ 9-11. Owners' experts also explained, based on their personal experiences from that period that many working in this field viewed the successful production of even one monomeric polypeptide in a host cell to be a significant accomplishment. See, e.g., McKnight II ¶¶ 8-14; Declaration of Dr. Douglas A. Rice, [App. B401-451], ("Rice II") ¶¶ 28, 34; Declaration of Dr. Timothy John Roy Harris, [App. B452-548], ("Harris I") ¶ 36.

Indeed, regardless of the type of protein being made, the literature shows that scientists employed the same conceptual approach of producing only one desired polypeptide at a time in a genetically transformed host cell. See McKnight II ¶ 5.

The recombinant production of insulin provides perhaps the best illustration of this prevailing mindset.[2] As of April 1983, insulin was the only "multimeric" protein that had been made using genetic engineering.[3] There were two known ways for making insulin in April 1983, and both involved producing only one insulin polypeptide at a time in a host cell and later assembling the insulin multimer in a test tube.[4] Harris II ¶ 14. In other words, to produce even this very simple multimeric protein before April 1983, scientists followed the same conceptual approach that had been used to produce every other eukaryotic protein before April 1983 – produce only one desired polypeptide at a time in a host cell.

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[2] Two of the inventors in this case (Drs. Riggs and Heyneker) also played a central role in the pioneering work that led to the successful production of insulin using genetic engineering.

[3] Insulin is a small (~5 kD), simple "multimeric" protein made up of two short polypeptide chains. By contrast, an immunoglobulin molecule is a large (e.g., ~150 kD) complex assembly of four large, distinct polypeptide chains having numerous intra- and inter-chain covalent linkages. See '415 patent, col. 3, lns. 15-61; McKnight II ¶ 10.

[4] See McKnight ¶¶ 10-11. Under one approach, each insulin chain was made in a separate host cell, and then the individually produced chains were combined in a test tube to form the multimeric insulin complex. Under the other approach, a single polypeptide precursor to insulin was made in a host cell, isolated, and digested with an enzyme to obtain the two insulin chains. Then, the two chains were used to form the multimeric insulin structure in a test tube.

(b) The Separate and Very Different Cabilly Inventions

(i) The Cabilly I Patented Invention (the '567 Patent)

On March 28, 1989, after nearly 3.5 years of prosecution, and nearly six years after filing, the Office issued the '567 patent. The '567 patent claimed one of two scientific breakthroughs disclosed in the Cabilly patents – the creation of a new type of immunoglobulin chain structure made possible only by exploiting genetic engineering techniques. This new type of immunoglobulin chain structure – a "chimeric" immunoglobulin polypeptide – combined variable region sequences of a heavy or light chain from an immunoglobulin source (e.g., mouse) with constant region sequences from a different immunoglobulin source (e.g., human). In issuing the '567 claims, the PTO concluded that this new type of immunoglobulin structure represented a patentable advance over the prior art.

The '567 patented invention embodied conventional thinking in one respect – it embraced the conventional approach of producing only one polypeptide at a time in a transformed host cell. Specifically, as illustrated by claim 1, the '567 patented method comprises:

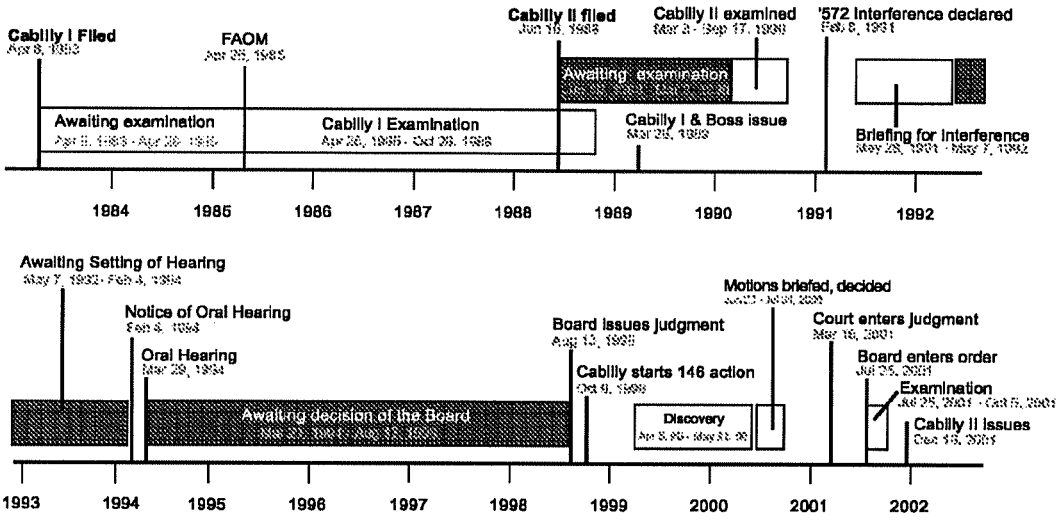
- preparation of one foreign DNA sequence encoding one polypeptide (i.e., a "heavy or light" chimeric immunoglobulin chain) ['567 claim 1, step (a)];
- transformation of a host cell with this single DNA sequence linked to a "replicable expression vector operably linked to a suitable promoter" ['567 claim 1, steps (b) and (c)];
- culturing of the transformed host cell ['567 claim 1, step (d)], and
- recovery of the single polypeptide produced by the transformed host cell (i.e., "recovering the chimeric heavy or light chain from the host cell culture.") ['567 claim 1, step (e)].

Thus, by following the recited steps of the '567 claims, one obtains only one desired polypeptide (i.e., a chimeric heavy immunoglobulin chain, or a chimeric light immunoglobulin chain) from a transformed host cell.

(ii) The Cabilly II Patented Invention (the '415 Patent)

The '415 patent issued on December 18, 2001 from a continuation application (the '419 application) filed on June 10, 1988. As illustrated below, for over eight years of the

approximately 13.5 year pendency of this application, the application was awaiting action by the PTO.



During the remaining 5.5 years of its pendency, the application was involved in an interference proceeding (i.e., Interference No. 102,572), a district court action under 35 U.S.C. § 146, and two phases of ex parte examination (i.e., before and after the interference and § 146 proceedings).

The '415 patent claims the second pioneering advance described in the Cabilly patent disclosure. The '415 claims require production of a multimeric immunoglobulin structure using a single genetically engineered host cell that independently expresses foreign DNA sequences encoding two very different eukaryotic polypeptides – the heavy and light chains of an immunoglobulin. The '415 claimed approach was a dramatic departure from conventional thinking in the field of genetic engineering in April 1983. Up to that point, scientists had attempted production of only one desired polypeptide at a time in a host cell –the same approach embodied in the '567 patent claims.

The inventors' work was the first report of a host cell that had been genetically engineered to produce two different desired eukaryotic polypeptides in a single host cell. It also was the first report of the successful recombinant production of a functional multimeric protein

having the structural complexity of an immunoglobulin. The Cabilly inventors' approach in each case sharply diverged from the conventional thinking in the field.

First, it abandoned the "one polypeptide-one host cell" strategy that had been uniformly followed by those working in the field prior to April 1983. See, e.g., McKnight II ¶ 16, 37, 46-47, 55. The '415 claimed invention instead required that, in addition to whatever DNA sequences were needed to identify successfully transformed host cells and to apply selective pressure on them, two other foreign DNA sequences be independently expressed by the cell. Second, it took a new and previously untested approach of producing the constituent polypeptides of a multimeric protein in a single host cell, instead of the simpler and more controlled approach of producing each polypeptide in a separate host cell and forming the multimeric protein complex in a test tube. See McKnight II ¶¶ 8-11.

Instead of recognizing these significant departures from conventional thinking in April 1983 for what they were, hindsight appears to have seduced the Examiner to overlook or discount their significance. In reality, the '415 invention and its proof of successful production of a functional antibody both revolutionized and surprised the industry.

(c) Four Distinct Reasons Mandate Reversal of the Rejections

The final rejection must be reversed because the evidence does not support the factual findings necessary to establish a prima facie showing of obviousness-type double patenting. See In re Rouffet, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453, 1455 (Fed. Cir. 1998) ("On appeal to the Board, an applicant can overcome a rejection by showing insufficient evidence of prima facie obviousness."). To the contrary, the evidence, when assessed correctly, establishes that the '415 claimed approach of producing a multimeric immunoglobulin structure was a patentably distinct advance over the '567 claimed method of producing a single chimeric immunoglobulin polypeptide.[5]

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[5] The focus of the Examiner's rejection is the failure of the '567 patent to "teach co-expression of light and heavy antibody chains in a host cell." Final Action at 14. Accordingly, Owners' have addressed the rejection with regard to representative claim 1. However, for the reasons stated previously to the Examiner and recited in detail in this brief, all of the claims are patentably distinct from the '567 patent and the cited prior art.

(i) The Prior Art Does Not Disclose or Suggest All of the Elements Required by the '415 Claimed Invention

Under well-established law, every element in a claim must be given weight when assessing the claimed invention as a whole, including in an obviousness-type double patenting analysis. See General Foods Corp. v. Studiengesellschaft Kohle mbH, 972 F.2d 1272, 1280, 23 U.S.P.Q.2d 1839, 1845 (Fed. Cir. 1992) (holding that the obviousness-type double patenting analysis conducted by the trial court "violate[d] the fundamental rule of claim construction, that what is claimed is what is defined by the claim taken as a whole, every claim limitation . . . being material."); see also Schenck v. Nortron Corp., 713 F.2d 782, 785; 218 U.S.P.Q. 698, 700 (Fed. Cir. 1983); M.P.E.P. § 2143.03.

The record shows that the Examiner has been laboring for more than three years to find in the '567 claims or in the teachings of the prior art all of the required elements of the '415 claimed invention. Simply put, they are not there. Instead, the substantial evidence of record in this reexamination proceeding demonstrates that, as of April 1983, the '567 claims do not define, and the prior art does not show or suggest:

- a single host cell transformed with DNA sequences encoding two or more different desired eukaryotic polypeptides of any kind, much less two different immunoglobulin polypeptides (see subpart (i) of claim 1 of the '415 patent);
- the successful independent expression of foreign DNA sequences encoding two different desired eukaryotic polypeptides of any kind in a single host cell, much less two different immunoglobulin polypeptides (see subpart (ii) of claim 1 of the '415 patent); and
- making a multimeric immunoglobulin structure using light and heavy chains that have both been produced using recombinant DNA techniques (see lines 1-5 and subpart (ii) of claim 1 of the '415 patent).

In other words, nothing in the eight references the Examiner has cited to support his rejection, or which could be drawn from the general knowledge in the field of genetic engineering in April 1983, would have led a person of ordinary skill to abandon the conventional "one polypeptide in a host cell" approach of the '567 claims, and instead pursue the conceptually distinct, significantly more challenging, and scientifically untested way of producing a multimeric immunoglobulin structure required by the '415 claims. This is not a case where one could

predictably combine known "prior art elements" to achieve the '415 claimed invention in April 1983.

(ii) The Prior Art Leads Away from the '415 Claimed Approach of Producing a Multimeric Immunoglobulin Structure

The record shows instead that, in April 1983, the '415 claimed invention used an approach for producing a complex multimeric protein that fundamentally departed from the path established by the prior art, the conventional thinking in the field, and, critically, the '567 claimed invention. The '415 claimed method represented a paradigm shift in the field of genetic engineering. Indeed, the Office observed "the production of recombinant antibodies was a milestone in molecular biology"[6] in finding the Axel patent disclosure insufficient to support claims to producing antibodies in any manner using genetic engineering techniques in 1997. The industry's acknowledgement of this scientific breakthrough is shown by the extensive licensing of the '415 patent independent from that of the '567 patent. See Declaration of Dr. Fintan E. Walton, [App. B1233-1242], ("Walton") ¶¶ 26-28, 34.

When the prior art is portrayed accurately, it shows that if a person of ordinary skill in the art wanted to produce a multimeric immunoglobulin structure in April 1983, that person would not have taken the path required by the '415 claims. As Dr. McKnight succinctly explained:

> I believe these references would have told a person of ordinary skill in the art in April 1983 to not attempt to produce an immunoglobulin molecule by expressing two different DNA sequences encoding the heavy and light chains in one transformed host cell. Instead, I believe the references suggested taking the opposite approach. ...

McKnight II ¶ 8. In other words, in April 1983, the prior art tells the person of ordinary skill to not modify the approach set in the '567 claims, but instead to follow it by first producing the heavy and the light immunoglobulin chains in separate host cells and, if those efforts are successful, attempting to assemble the separately produced chains into the desired multimeric immunoglobulin structure in a test tube. See McKnight II ¶ 8.

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[6] See Patent Application No. 08/395,520 (Axel), Paper No. 10, Office Action mailed March 20, 1997, [App. B1644-1650] at 6. (emphasis added). The Examiner anchors his rejections of the '415 claims on the Axel disclosure, which is the same between the Axel '520 application and the cited Axel patent in this case.

In fact, this "opposite approach" is what is expressly called for in the only two publications cited by the Examiner that are actually focused on producing immunoglobulin multimers – Kaplan and Moore. Each of these references outlines a plan which consists of producing heavy and light chain polypeptides in separate host cells, isolating each chain from its respective cell culture, and assembling the multimeric immunoglobulin structure using these individually produced chains in a test tube. McKnight II ¶¶ 12-13. It is also the only approach that: (i) starts with the result actually required by the '567 claims (i.e., compositions containing an isolated light or an isolated heavy chain polypeptide, not both), (ii) employs the "DNA I + DNA II" strategy described in Axel, and (iii) employs the same approach used to produce insulin using genetic engineering techniques (the only multimeric protein made before April 1983). See McKnight II ¶¶ 10-11; Harris II ¶ 14.

Moreover, changing the '567 claimed "one-at-a-time" approach to instead follow the '415 claimed approach would effectively negate the benefits identified in the Cabilly disclosure as being solely associated with the '567 claimed invention. The specification, for example, points out that producing chains in separate host cells – the subject of the '567 claims – yields individual chain compositions that can be used to assemble various types of combinations of heavy and light chains in a more controlled manner. See '567 at col. 14, line 65 - col. 15, line 19; see also Declaration of Dr. Arthur D. Riggs, [App. B1002-1187], ("Riggs") ¶¶ 3-18, 32. Producing the chains together in one host cell as required by the '415 claims would nullify the advantages of the '567 claimed invention expressly identified throughout the common disclosure of the patents.[7] See, e.g., Esai Co. Ltd. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 1358, 87 U.S.P.Q.2d 1452, 1456 (Fed. Cir. 2008).

Thus, the '567 claimed invention, taken in view of the individual and collective guidance of the cited references, and considered in light of the prevailing knowledge held by a person of ordinary skill in the art in April 1983, would have told a person of ordinary skill to follow a different path to produce a multimeric immunoglobulin structure than what is required by the '415 claims. See KSR Int'l. Co. v. Teleflex Inc., 127 S. Ct. 1727, 1739-40, 82 U.S.P.Q.2d 1385,

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[7] See, e.g., '415 patent at col. 4, lines 53-62; col. 12, lines 58-65; col. 13, lines 54-67; col. 14, lines 20-39; col. 14, lines 45-50; col. 14, line 67 to col. 15, line 9 and col. 15, line 60 to col. 16, line 2; col. 14, lines 45-50.

1395 (2007) (noting the principle that "when the prior art teaches away from a combination, that combination is more likely to be nonobvious"); In re ICON Health and Fitness, Inc., 496 F.3d 1374, 1381, 83 U.S.P.Q.2d 1746, 1751 (Fed. Cir. 2007) ("[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.").

(iii) The '567 Claims and the Cited References Do Not Show that the '415 Claimed Invention Could Have Been Predictably Achieved in April 1983

Several experts with actual experience in the field of the invention in April 1983 explained that those references cited by the Examiner that include experimental results show a significant amount of unpredictability in achieving success in simpler experiments than what is required by the '415 patent claims. See, e.g., McKnight II ¶¶ 6-7, 30-34; Declaration of Steven Lanier McKnight, [App. B197-374], ("McKnight I") ¶¶ 83-86; Declaration of Michael Botchan, [App. B585-780], ("Botchan") ¶¶ 72, 98, 99, 103; Rice II ¶ 16. When these experts were asked whether a person of ordinary skill in the art would have believed that producing a complicated multimeric protein structure (i.e.,, the immunoglobulin multimers required by the '415 claims), using an approach (i.e., expressing, in a single host cell, foreign DNA sequences encoding both the heavy and light chain components of the immunoglobulin multimer) which had never been used before April 1983, could have been predictably achieved based on the '567 patented invention and what is disclosed in these publications, they uniformly answered "no." See McKnight II ¶¶ 6-7, 30-34, 37; McKnight I ¶¶ 83-88, 91, 104; Harris II ¶¶ 23-28, 57-59; Botchan ¶¶ 67-68, 71-72, 104-105; Rice II ¶¶ 11-16. The evidence thus shows that a person of ordinary skill would have viewed the '415 claimed invention as being more than simply a "predictable extension" of the '567 claims and the teachings in the cited references in April 1983. See KSR, 127 S. Ct. at 1731, 82 U.S.P.Q.2d at 1396 ("a court must ask whether the improvement is more than the predictable use of prior art elements");[8] Ortho-McNeil Pharmaceuticals, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358, 1364-1365, 86 U.S.P.Q.2d 1196, 1201-1202 (Fed. Cir. 2008).

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[8] See also KSR, 127 S. Ct. at 1740, 82 U.S.P.Q.2d at 1395, where the Court distinguished, on the one hand, precedent finding inventions to be non-obvious where they did not consist of

(iv) The Strong Evidence of Secondary Considerations Negates the Asserted Obviousness of the '415 Claims

This record also contains substantial – and unchallenged – evidence of secondary indicia of non-obviousness. This evidence, which is attributable solely to the '415 claimed invention, includes extensive licensing of the '415 patent claims – independent of licensing of the '567 claims – by many sophisticated licensees. Walton ¶ 28. Several entities using the '415 patented invention pay royalties solely under this patent. Other entities have licensed both the '415 and '567 patents, but have licensed each patent independently, and likewise have paid royalties under each patent independently. In fact, one of those entities has affirmatively stated that, while it held licenses under both patents, it paid royalties only under the '415 patent. See Walton ¶ 27, footnote 5. This widespread industry acquiescence to the validity of the '415 patent is powerful evidence of the validity of the '415 patent, particularly in reference to the '567 patent.

The evidence also shows that the '415 patented invention enjoys tremendous commercial success. Specifically, Dr. Walton, an expert in patent valuation and licensing, analyzed the revenues paid to the Owners under the '415 patent, and has concluded the significant revenues solely attributable to the '415 patent demonstrate that the '415 patented invention is enjoying significant commercial success, including relative to the '567 patented invention. See Walton ¶¶ 21-36, 44-46.

(d) The Examiner's Rejection Must Be Reversed as Unsupported by the Evidence and the Controlling Law

(i) Applicable Law

Obviousness in a double-patenting context is assessed using the same general approach to assessing obviousness under 35 U.S.C. § 103. See M.P.E.P. § 804(II)(B)(1). Obviousness-type double patenting, like obviousness, is a legal question to be determined on the basis of underlying facts. See M.P.E.P. § 804(II)(B)(1) ("The conclusion of obviousness-type double patenting is made in light of these factual determinations."); Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 U.S.P.Q. 459, 466. See also KSR, 127 S. Ct. at 1736, 82 U.S.P.Q.2d at 1391

"known" elements and where their outcome was not reasonably predictable, from precedent, on the other hand, where all elements of claimed inventions were well known and where their combination yielded predictable outcomes.

(affirming use of the Graham framework for assessing obviousness). The primary distinctions in a double-patenting context are (i) the claims of the earlier patent serve as the reference point for the obviousness analysis rather than the prior art, and (ii) the earlier patent may not be considered as information known in the prior art.[9]

The analysis thus must begin with a comparison of the '567 claimed invention to the '415 claimed invention. Once the differences between the claimed inventions are accurately identified and appreciated, the '415 claimed invention as a whole must then be evaluated. Only if the claimed invention as a whole would have been considered obvious by a person of ordinary skill in the art in April 1983 -- based on the '567 patented invention, the prior art, and the knowledge available at the time of the invention -- can it be held unpatentable for obviousness-type double patenting. See General Foods, 972 F.2d at 1280, 23 U.S.P.Q.2d at 1845; W.L. Gore & Assoc., Inc. v. Garlock, Inc., 721 F.2d 1540, 1548, 220 U.S.P.Q. 303, 309 (Fed. Cir. 1983) ("In determining obviousness . . . [a] court's restriction of a claimed multi-step process to one step constitutes error."); Schenck, 713 F.2d at 785, 218 U.S.P.Q. at 700. In other words, the invention may not be evaluated by considering its separate and distinct elements in isolation. Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1275, 69 U.S.P.Q.2d 1686, 1690 (Fed. Cir. 2004).

To establish a prima facie case, the Examiner must not only accurately determine what the claims define and what the prior art teaches, he must also explain why the facts establish, prima facie, that the '415 claimed invention would have been considered obvious to a person of ordinary skill in the art just prior to the effective filing date of the two patents. See Ex parte Clapp, 227 U.S.P.Q. 972, 973 (Bd. Pat. App. & Interf. 1985) ("To support the conclusion that the claimed [invention] is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed [invention] or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references.").

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[9] As explained below in section (d)(viii), the Examiner legally erred by repeatedly treating the common Cabilly patent disclosure and the '567 claims as though they were prior art, citing them for their "teachings" "suggestions" and "motivation."

Obviousness cannot be established by simply finding the distinctions between a claimed invention and a reference anywhere, and in any context, in the prior art. As the Supreme Court has explained, "[t]his is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." KSR, 127 S. Ct. at 1741, 82 U.S.P.Q.2d at 1396. See also In re Wesslau, 353 F.2d 238, 241, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965); In re Fine, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention"); Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 448-49, 230 U.S.P.Q. 416, 420 (Fed. Cir. 1986) (holding that the district court, by failing to consider a prior art reference in its entirety, ignored portions of the reference that led away from obviousness); Ex parte Honsberg-Riedl, 2007 WL 3827797 **5-7 (Bd. Pat. App. & Interf. 2007) (reversing rejection based on Examiner's picking and choosing isolated aspects of prior art reference, citing In re Wesslau in support).

(ii) The Final Rejection and the Underlying Record of Examination

The final rejection rests on the fourth distinct theory of "obviousness-type" double patenting asserted by the Examiner in this reexamination proceeding. With each new theory, the Examiner substantially changed his interpretation of what the claims of the two patents define, and what the references would have taught or suggested to a person of ordinary skill in April 1983. Owners have responded to the Examiner's repeatedly shifting positions by systematically disassembling each of the rejections, identifying the factual and legal errors made by the Examiner, and supporting their arguments with evidence in the form of declarations under 37 C.F.R. § 1.132 from qualified experts having relevant personal experiences and knowledge from April 1983. See Owner replies dated November 2005, October 2006, May 2007, June 2008, and associated declarations. As a consequence, there is a substantial record of evidence in support of patentability of the '415 claims in this case.

The Examiner's latest theory of obviousness-type double patenting is set forth in his rejection of claims 1-4, 11, 13, 15-18, 21, 23-25, and 33 of the '415 patent (pages 10 to 16 of the Final Action), and in his further rejection of dependent claims 5-10, 12, 14, 19-20, 22, 26-32, and

34-36 (pages 16 to 20 of the Final Action). All of the Examiner's rejections rest on the following three conclusions he has reached:[10]

(1) "The reference Cabilly 1 patented invention differs from the instant patent since it fails to teach the co-expression of heavy and light antibody chains in a host cell." Final Action at 12.

(2) "One of ordinary skill in the art would have been motivated to express, in a single host, light and heavy immunoglobulin chains (using one or two vectors) when viewing the reference Cabilly 1 patented invention in light of the prior art." Id. The prior art used to reach this conclusion consists of Axel, Rice, Kaplan, and Dallas. Final Action at 12-14.

(3) "The prior art provides further motivation to make an active antibody with a reasonable expectation of success." The "prior art" used to support this assertion consists of Ochi/Oi et al. (1983) Proc. Nat'l. Acad. Sci., 80: 825-829, [App. B155-159], ("Oi"), Valle 1981, Deacon and Moore. Final Action at 14.

The Examiner's conclusions rest on an incomplete understanding of the differences between the two patents, substantial factual errors regarding the teachings of the prior art, and a legally improper analysis for obviousness-type double patenting. Consequently, the rejections must be reversed.

(iii) The Patentably Distinct Inventions of the '415 and '567 Patents

A. Three Important Differences Between the Claimed Inventions

Properly construed, the '415 and '567 claims define inventions that differ in at least three ways that a person of ordinary skill in the art would have considered important in April 1983.

- First, the '415 claims require a host cell transformed with DNA sequences encoding two different polypeptides (i.e., at least the variable domain of a light immunoglobulin chain and at least the variable domain of a heavy immunoglobulin chain) (see step (i) of claim 1). The '567 claims require that a host cell be transformed with a DNA sequence encoding only one immunoglobulin polypeptide (see, e.g., '567 Claim 1, step (a), "preparing a DNA sequence encoding a chimeric immunoglobulin heavy or light chain").

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[10] The focus of the Examiner's rejection is the failure of the '567 patent to "teach co-expression of light and heavy antibody chains in a host cell." Accordingly, Owners have addressed the rejection with regard to representative claim 1 of the '415 patent. However, for the reasons stated previously to the Examiner and recited in detail in this brief, all of the claims are patentably distinct from the '567 patent and the cited prior art.

- Second, the '415 claims require a host cell that produces two different desired polypeptides (i.e., heavy and light chain polypeptides) "as separate molecules in said transformed single host cell" (see step (ii) of claim 1). (emphasis added). Because there is no requirement in the '567 claims for production of more than one immunoglobulin polypeptide, there is no mention of, much less a requirement for, production of the heavy and light chain polypeptides as separate molecules in a single transformed host cell.

- Third, the '415 claims require production of a multimeric immunoglobulin structure using heavy and light chain polypeptides that have been produced in a single transformed host cell (see lines 1-5 and step (ii) of claim 1). By contrast, there is no requirement in the '567 claims that the individual chimeric heavy or light chain polypeptide that is recovered be assembled into any different structure, such as a multimeric immunoglobulin structure according to the '415 patent. In other words, the two claims require significantly different end-points.

Each of these different features of the '415 claimed invention had no precedent or analogy in the field of genetic engineering in April 1983, and a person of ordinary skill in the art would have considered each to be a significant departure from the conventional "one polypeptide at a time" approach embodied in the '567 claimed invention.

A proper obviousness-type double patenting analysis requires that all of these differences be considered together when evaluating the claimed invention as a whole. For example, in a similar fashion to what the Examiner is attempting to do in this case, in Schenck, the accused infringer attempted to prove the claims obvious by focusing the inquiry on a single difference between the claimed invention and the prior art, and then showing that this one difference alone would have been obvious. The Federal Circuit soundly rejected this approach, holding:

> That effort is not proper under the statute, which requires that an invention be considered "as a whole," 35 U.S.C. § 103. As Judge Nixon recognized, "the emphasis on nonobviousness is one of inquiry, not quality". Graham v. John Deere Co., 383 U.S. 1, 86 S. Ct. 684, 15 L.Ed.2d 545 (1966). The inquiry here establishes that the present invention includes the inventor's elimination of the need for damping. Because that insight was contrary to the understanding and expectations of the art, the structure effectuating it would not have been obvious to those skilled in the art. United States v. Adams, 383 U.S. 39, 86 S. Ct. 708, 15 L.Ed.2d 572 (1966).

Schenck, 713 F.2d at 785, 218 U.S.P.Q. at 700. Similarly, in this case, instead of assessing the '415 claimed invention as a whole, the Examiner has dissected it into discrete elements, considered only some of those elements in isolation rather than in the context required by the

claimed invention as a whole, and concluded the "differences" he sees between the '567 and '415 claimed invention were "obvious." This approach, prohibited by law, has fundamentally skewed the Examiner's analysis and his conclusions of obviousness.

B. The Examiner Fails to Properly Identify and Appreciate the Differences Between the Host Cells Required by the '415 and '567 Claimed Inventions

Two of the important differences between the '415 and '567 claimed inventions concern the nature of the genetically engineered host cells that are required. Specifically, the '415 claims require: (i) a single host cell transformed with foreign DNA sequences encoding two different immunoglobulin polypeptides, and (ii) that the host cell independently express the foreign DNA sequences to yield two polypeptides produced as "separate molecules" in the cell. The '567 claims, by contrast, require a host cell that has been genetically engineered with one foreign DNA encoding one chain and which produces only one desired polypeptide.

The experts explained why the host cells required by the '415 claims (and what must be done to produce them) are not analogous, much less equivalent, to the host cells required by the '567 claimed invention or disclosed in the prior art. McKnight II ¶ 4; Harris I ¶ 9-10; Harris II ¶¶ 29-34; Botchan ¶¶ 104, 105; Rice II ¶ 39. They also explained that, like the case of insulin, approaching production of the immunoglobulin multimer by engineering different host cells to produce each of its required constituent polypeptides one at a time would break down the process into more manageable steps. See, e.g., McKnight II ¶¶ 7-16. As Dr. McKnight explained, "[o]nly this approach would have been consistent with the prevailing mindset in April 1983 to produce one eukaryotic polypeptide at a time in a transformed host cell." McKnight II ¶ 8.

The fact that every reported example of the successful genetic engineering of a host cell to produce a desired eukaryotic protein by April 1983 employed the same conceptual approach – including the approach embodied in the '567 claims –operates to confirm that this was the well-accepted understanding in the field at that time. See McKnight II ¶ 9; Harris II ¶¶ 13-16. Against this backdrop, a person of ordinary skill in the art would have viewed the host cell requirements of the '415 claims – which had no precedent or analogy in the prior art – to be an important difference from the requirements of the '567 claims.

Rather than recognizing the importance of these differences, the Examiner states simply that: "the reference Cabilly 1 ['567] patented invention differs from the instant patent since it fails to teach the co-expression of light and heavy antibody chains in a host cell." Final Action at 12. But the Examiner's varied explanations of what "co-expression" means reveals that he does not understand what this difference between the '415 and '567 claimed inventions is, and certainly does not appreciate its significance in April 1983.

For example, the Examiner portrays the "co-transformation" experiments in Axel as being equivalent to the requirements of the '415 claims, asserting that Axel teaches "co-transforming more than one desired gene for making proteinaceous materials which include multimeric proteins, such as interferon."[11] Final Action at 29. This view is grounded on a fundamental scientific mistake the Examiner has made. Specifically, the Examiner believes the Axel experiments are analogous to the '415 patented invention because he believes that:

> *Cotransformation* means the process for carrying out transformations of a recipient cell **with more than one different gene**. Axel '216 patent col. 4, lines 23-25 (with emphasis). Cotransformation is synonymous with coexpression.

Final Action at 29. Cotransformation is not synonymous with coexpression. As Dr. McKnight pointed out, "transformation" means the stable introduction into a host cell of the foreign DNA. By contrast, "expression" refers to the steps that occur after the foreign DNA has been introduced into the cell; namely, "transcription" to generate mRNA and "translation" of the mRNA to produce the polypeptide. McKnight II ¶¶ 17-23. And Axel itself reveals the importance of this distinction, by disclosing the successful "cotransformation" of a host cell with two foreign DNA sequences but unsuccessful "coexpression" of those two sequences. See id. See also infra at § (d)(iv)(C)(III).

A person of ordinary skill would have immediately recognized that the "co-transformation" experiments described in Axel – which use only two DNA sequences, one encoding a selectable marker and the other encoding a single desired polypeptide – are not analogous to the more complex genetic manipulations required to engineer a host cell that

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[11] The Examiner mistakenly calls interferon a "multimeric" protein. See McKnight II ¶ 21, note 14.

independently expresses foreign DNA sequences encoding two different desired eukaryotic polypeptides, as the '415 claims require. McKnight II ¶¶ 17-23; Botchan ¶¶ 48-53. Instead, the Axel work embodies nothing more than the conventional "one polypeptide per host cell" strategy reflected throughout the prior art in April 1983. Harris II ¶¶ 44, 48; Botchan ¶¶ 50-51; McKnight II ¶¶ 16-23.

Similarly, the Examiner characterizes the work in Rice as demonstrating "the successful expression of both heavy and light chains in a host with subsequent assembly into immunoglobulins." Final Action at 13. Here, the Examiner errs by equating the normal, continued expression by a cell of one of its native (endogenous) genes with the successful introduction into and expression of a foreign gene in a host cell. As Dr. McKnight explained:

> A scientist working in this field would not equate a cell's expression of its own endogenous genes to be equivalent to the introduction and expression of a foreign DNA sequence in that organism. If this were the case, genetic engineering would have been a trivial task. Thirty years of experience demonstrates the contrary.

McKnight I ¶ 82 (emphasis added). This reveals that the Examiner does not understand what a person of ordinary skill would have to do to achieve the latter result (i.e., genetically transform the host cell and achieve successful expression of the foreign gene) relative to achieving the former (i.e., doing nothing and relying on natural expression of an endogenous gene).[12]

The Examiner also summarily dismisses the substantial scientific distinctions that exist between expressing foreign DNA sequences in a transformed host cell, and translating injected messenger RNA (mRNA) fractions in a frog oocyte (i.e., Deacon, Valle 1981). The Examiner does so despite the testimony of experts explaining that the two processes are in no way equivalent. Declaration of Dr. Alan Colman, [App. B781-1001], ("Colman") ¶¶ 15, 23-24; see also Harris II ¶ 95; McKnight I ¶¶ 105, 107-108; McKnight II ¶¶ 49-54; Botchan ¶¶ 86, 89-94.

All of these errors show that the Examiner does not understand this difference between the '415 and '567 claimed inventions. It also shows that he does not appreciate what would have been necessary to genetically engineer a single host cell to produce heavy and light

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[12] Similar errors are made by the Office with regard to what is shown in the Ochi and Oi publications. See, e.g., Botchan ¶¶ 95-99, 103; Harris II ¶¶ 84-85.

immunoglobulin polypeptides in April 1983, relative to engineering a host cell to produce only one polypeptide. The Examiner's interchangeable use of terms like "co-transformation" and "co-expression" and his reliance on scientifically unsupported analogies are primary reasons why he has incorrectly concluded that this important difference between the '415 and '567 patented inventions is insubstantial, and therefore obvious.

C. The '415 Invention Requires a Substantially Different Product Made by a Substantially Different Process

The '567 claims require the performance of a number of steps, the endpoint of which is the recovery of an isolated single immunoglobulin chain. See '567 Claim 1, step (e) ("recovering the chimeric heavy or light chain from the host cell culture"). From this point, achieving the '415 claimed invention is not simply a matter of taking an additional step (e.g., expression of another DNA sequence). Instead, the '415 claims require that the person of ordinary skill to abandon the conceptual approach embedded in the '567 claims, and to adopt a previously untested approach. McKnight II ¶¶ 5, 34; Harris II ¶¶ 29-33.

Critically, the Examiner never directly explains or even addresses the question why a person of ordinary skill in the art would have done this. Instead, he reasons simply that production of an immunoglobulin multimer would have been seen as a "preferred utility" by a person of ordinary skill in the art considering the '567 claims. See Final Action at 12, 14-15, 23-25. However, the existence of this "preferred utility" for the individually produced chains of the '567 patent – a conclusion the Examiner alone draws from the Cabilly specification – does not answer the question why the '415 claimed way of making an immunoglobulin multimer would have been considered obvious in April 1983 based on the '567 claimed way of making a single immunoglobulin polypeptide, and prior art uniformly showing scientists following the same "one desired polypeptide in a host cell" approach.

The '567 claims do not, in fact, require the production of a multimeric immunoglobulin structure; they require production of only a single immunoglobulin polypeptide. See '567 Patent claims. And, as Dr. McKnight explained, if one of ordinary skill, after considering the '567 claims, were inspired to produce a multimeric immunoglobulin structure, that person would have first prepared the heavy and light chains in separate host cell cultures, as the '567 claims require.

McKnight II ¶¶ 14-16. Then, after isolating and purifying each separately produced chain, the person would have attempted to form the immunoglobulin multimer by combining the chains in a test tube. In other words, the person of ordinary skill in the art, after considering the '567 claims, would have followed the prophetic roadmap set forth in the Kaplan and Moore patents cited by the Examiner. See McKnight II ¶ 8; see also, infra, § (d)(iv)(E).

The fact that heavy or light immunoglobulin chains produced according to the '567 claims can be used to produce an immunoglobulin molecule is ultimately irrelevant. The '415 claims are not drawn generally to immunoglobulin multimers, but to a particular way of making those immunoglobulin multimers. And, as the record abundantly shows, the way the '415 claims require the immunoglobulin multimer to be made was a dramatic departure from the way in which the '567 claims, the prior art, and conventional thinking in April 1983 called for production of a eukaryotic proteins using genetic engineering techniques.

The Examiner also commits a significant legal error in evaluating whether one could have successfully produced a multimeric immunoglobulin structure in April 1983 without regard to how the two chains were produced. To support his belief that a person of ordinary skill would believe that an immunoglobulin multimer could have been predictably produced in April 1983, the Examiner cites references involving microinjecting mRNA from a B-cell into a frog oocyte (Deacon and Valle 1981), or in hybridoma cells transformed with a single foreign light chain obtained from its parental line that was successfully expressing its endogenous (native) immunoglobulin genes. See Final Action at 13-15, 31-33, 37-38, 40-43. The experts explained why results in these types of experiments would not have been extended to a process where both the heavy and the light chains must be produced by expression of two different foreign (exogenous) DNA sequences in the same transformed host cell. See, e.g., Colman ¶¶ 15, 29, 30, 32; Rice II ¶¶ 33-37; Botchan ¶¶ 68-69, 85-86, 89, 91-94; McKnight I ¶¶ 103-105, 111-112; McKnight II ¶¶ 33-34. The Examiner's approach of assessing the immunoglobulin assembly required by the '415 claims in isolation from how the two chains are produced violates the well-established rule that the claimed invention as a whole must be assessed. See Schenck, 713 F.2d at 785; 218 U.S.P.Q. at 700 ; General Foods Corp., 972 F.2d at 1280, 23 U.S.P.Q.2d at 1845 (Fed. Cir. 1992).

D. The Examiner Mistakenly Relies on Geneva Pharmaceuticals

The Examiner mistakenly relies on Geneva Pharmaceuticals Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 68 U.S.P.Q.2d 1865 (Fed. Cir. 2003) to support his belief that the "utility" of individually produced chains is relevant to the question of obviousness in this case. See Final Action at 23-24. In Geneva, the Federal Circuit found double patenting by reasoning that "a claim to a method of using a composition is not patentably distinct from an earlier claim to the identical composition in a patent disclosing the identical use." 349 F.3d. at 1385-1386, 68 U.S.P.Q.2d at 1875. In Geneva, unlike here, the second patent claimed the one and only use for the composition that was claimed in the first patent. 349 F.3d at 1385-86, 68 U.S.P.Q.2d at 1875 (explaining that "the [later] '720 patent claims nothing more than Fleming's [earlier] disclosed [single] utility as a method of using the Fleming compound."). Here, the common disclosure of the patents clearly differentiates the independent practical value of the two different approaches embodied in the '415 and '567 claims.[13]

The common patent disclosure begins by identifying production of individual heavy or light chains as a specific objective of the invention that is distinct from the goal of producing immunoglobulin multimers or other types of immunoglobulin constructs. See '567 patent, col. 5, lns. 32-36. See also Riggs ¶¶ 9, 19. It then explicitly identifies the benefits of producing individual chains in separate host cells. See Riggs ¶¶ 5-9. It also states that "[t]he ability of the method of the invention to produce heavy and light chains or portions thereof, in isolation from each other offers the opportunity to obtain unique and unprecedented assemblies of immunoglobulins, Fab regions, and univalent antibodies." See '567 patent at col. 13, lns. 28-32; see also, e.g., id. at col. 15, lns. 44-57 (describing hybrid antibodies); and id. at col. 16, lns. 33-54 (describing univalent antibodies). And, as Dr. Riggs explained, individual chains produced pursuant to the '567 claims have practical utilities independent of their use in producing immunoglobulin molecules or fragments. See Riggs ¶¶ 19-32.

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[13] It was unnecessary for the Examiner to consult the common specification because the terms of the '415 and '567 claims are clear, as the experts pointed out. The Examiner's actual use of the specification (i.e., for its "teachings") is legal error. See infra § (d)(3). Owners provide these observations on the common specification solely in response to the Examiner's errors.

Additional evidence reinforces these distinctions. For example, how the Office consistently treated claims following the form of the '415 and '567 patents prior to the present reexamination shows that the Office consistently viewed them to define patentably distinct inventions. See, infra, §(d)(vii). The pattern of independent licensing of the '415 and '567 patents by third parties also shows that the industry perceived the two different patented inventions to have a distinct character and status relative to each other. See, infra, §(d)(v).

The Examiner has presented no contrary evidence to rebut any of these points. Thus, in contrast to Geneva, the '567 and '415 patents define materially different methods each having independent practical utility and each producing materially different products. See Riggs ¶¶ 19-32; McKnight II ¶ 14-16. Geneva is irrelevant to this case.

(iv) The Examiner Does Not Establish a Prima Facie Case of Obviousness-Type Double Patenting, But Instead Rests on a Hindsight Reconstruction of the '415 Claimed Invention Using a Scientifically Incorrect Portrayal of the Prior Art

The Examiner cites eight different references in his effort to show that the '415 claimed approach of producing a multimeric immunoglobulin structure would have been "obvious" to a person of ordinary skill in the art in April 1983. The cited references, however, do not establish a prima facie case of obviousness of the '415 claims relative to the '567 claims because they collectively do not show or suggest all of the required elements of the '415 claimed invention, much less suggest this new approach to producing a multimeric immunoglobulin structure.

A. The Examiner Improperly Employed a Hindsight-Driven, Rather than Objective, Analysis of the Claims and Prior Art Teachings

The rejections show that the Examiner conducted his analysis by using the '415 claims as a template, and trying to find in the prior art what he (incorrectly) concluded were the differences between the '415 and '567 claims. The Examiner's use of a hindsight-driven, rather than objective, analysis of the '567 claims and the teachings of the prior art at the time of the invention is a profound legal error. See Graham, 383 U.S. at 36, 148 U.S.P.Q. at 474 (referencing the need to "guard against slipping into use of hindsight" and to "resist the temptation to read into the prior art the teachings of the invention [at] issue"); KSR, 127 S. Ct. at 1731, 82 U.S.P.Q.2d at 1397 (observing that it was important for the fact finder to be aware "of

the distortion caused by hindsight bias" and to "be cautious of arguments reliant upon ex post reasoning."); In re Rouffet, 149 F.3d at 1357, 47 U.S.P.Q.2d at 1457 ("rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be an illogical and inappropriate process by which to determine patentability.") (internal quotations omitted).

The risks of distortions caused by hindsight bias are significant in this case. Tremendous advances have been made in the fields of molecular biology and genetic engineering in the 25 years that have passed since the effective filing date of the '415 patent. Despite this fact, the Examiner repeatedly discards the §1.132 testimony of qualified experts who actually were working in the field of the invention in April 1983. In the place of this highly pertinent evidence, the Examiner uses his own interpretations of what he believes the cited references teach, and his hindsight-driven conclusions about the beliefs of a person of ordinary skill in the art.[14] Indeed, the Examiner's characterizations of the references often are not only inconsistent with those of the experts, they are contrary to the express teachings in the cited references and even to his own opinions expressed elsewhere in the Final Rejection.

B. The Examiner Ignored the "Collective" Teachings of the Cited References and the General Knowledge in the Field of the Invention in April 1983

Throughout this reexamination proceeding, the Examiner has emphasized the importance of considering the "collective" or "combined" teachings of the prior art. Appellants agree. Unfortunately, the Examiner has not followed his own admonitions.

Initially, the Examiner improperly dismissed a number of opinions offered by the experts based on his mistaken belief that the expert had not considered the "collective" teachings of the cited references. See, e.g., Final Action at 28, 37, 46. The record plainly shows that the experts expressed opinions about what the cited references would have taught the person of ordinary

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[14] See, generally, infra at §(d)(vi).

skill in the art in April 1983, both individually and collectively.[15] See, e.g., McKnight II ¶¶ 4-16, 37, 48-50, 55; McKnight I ¶¶ 3, 64, 78, 91, 102; Botchan ¶¶ 4, 104; Harris II ¶¶ 6, 78, 86; Rice II ¶¶ 38-45; Harris I ¶ 5. It also shows that they pointed to specific portions or aspects of the different references to illustrate how observations in the various references might have been considered together. See e.g., McKnight II ¶¶ 38-39, 55. And, several experts explained why a person of ordinary skill in the art would not have combined the eight cited references as the Examiner has in this case. See, e.g., Harris II ¶ 11, 12-28; Botchan ¶¶ 104-106; McKnight II ¶¶ 5-8, 55-56; Rice II ¶¶ 26, 38, 43.

The Examiner also failed to recognize that the "collective" teachings of the cited references in this case identify several distinct reasons why the '415 claimed invention would not have been seen as being "obvious" from the '567 claimed invention. For example, the experts explained that those cited references that include experimental results consistently showed unpredictability in simpler experiments than what is required by the '415 claimed invention. See, e.g., McKnight II ¶¶ 6-7, 30-34, 37, 48-54; McKnight I ¶¶ 83-88, 91, 99-102, 104-105, 107-108; Harris II ¶¶ 23-28, 57-59, 90-93; Botchan ¶¶ 67-68, 71-72, 83, 93-94; Rice II ¶¶ 11-16. The experts also pointed out that the references discussing concepts relevant to expression of eukaryotic genes or production of eukaryotic proteins all follow, rather than depart from, the approach of producing only one desired polypeptide at a time in a host cell. See, e.g., McKnight II ¶¶ 19-20, 30-31, 48; McKnight I ¶¶ 18, 26, 39, 66, 74, 80, 96, 111; Harris II ¶¶ 66, 68, 81, 83; Botchan ¶¶ 38, 48, 50, 63, 76-77, 97, 102; Harris I ¶¶ 21-22, 34, 41; Declaration of Douglas A. Rice, [App. B389-400], ("Rice I") ¶¶ 12-13; Declaration of Sidney Altman, [App. B1211-1232], ("Altman") ¶ 7; Declaration of Matthew P. Scott, [App. B1188-1210], ("Scott") ¶¶ 8, 12. The

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[15] The Examiner cites In re Keller, 642 F.2d 413, 208 U.S.P.Q. 871 (C.C.P.A. 1981) and In re Merck & Co., 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986) to justify his decision to disregard declaration evidence addressing what is described or taught by a cited reference. See, e.g., Final Action at 46. These cases actually hold that such testimony is to be accorded substantial deference because it goes to the predicate factual determinations required in an obviousness assessment. See In re Keller, 642 F.2d at 426, 208 U.S.P.Q. at 882, citing In re Carroll, 601 F.2d 1184 (C.C.P.A. 1979)("In Carroll this court concluded that the opinion of an expert on what the prior art taught was deserving of considerable deference under the circumstances of that case. The expert had critically reviewed the sole piece of prior art and totally discounted its value. The accuracy of the expert's views was supported by documentary evidence.").

Examiner simply ignored these important insights from the "collective" teachings of the references.

Additionally, the Examiner failed to properly consider the testimony of qualified experts explaining what the "general beliefs" of those working in the field of the invention was in April 1983. Under KSR, this type of evidence can play an important role in an obviousness assessment. KSR, 127 S. Ct. at 1740-41, 82 U.S.P.Q.2d at 1396 ("[o]ften, it will be necessary for a court to look to . . . the background knowledge possessed by a person having ordinary skill in the art"). In this case, this evidence is important because it reveals how those working in the field of the invention would have read the cited references, the nature of inferences they would have drawn from them (individually and collectively), and how they would have assessed the differences between the '415 and '567 claimed inventions relative to those understandings. Examples of observations made by these experts include:

- The conceptual design of the '415 claimed invention had never been attempted or even proposed at the time of the invention. [16]
- The method by which the much simpler insulin multimer had been produced illustrated the pervasive belief in the field of the invention that only one polypeptide should be produced at a time in a genetically engineered host cell. See, e.g., McKnight II ¶¶ 10-12; Harris II ¶ 14.
- The existence of a nearly exclusive focus of the field on producing monomeric proteins. Harris II ¶¶ 13-14; McKnight ¶¶ 9-11.

Additionally, the experts explained, based on their first-hand experiences of working in the field in April 1983, that a person of ordinary skill would have approached production of a multimeric protein in April 1983 by breaking the process into more manageable steps, particularly, by producing each polypeptide of the multimer one at a time, in a separate host cell. McKnight II ¶¶ 8-10. When the prior art is read accurately, and considered with this evidence of the general beliefs of those working in the field of the invention, it demonstrates that the '415 claimed invention would not have been obvious based on the '567 claimed invention in April 1983.

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[16] Dr. McKnight explained that he was not aware of a single reference that even suggested the concept of producing more than one eukaryotic polypeptide at a time in a host cell. See McKnight II ¶ 5. See also Harris II ¶ 16; Rice II ¶51.

C. Axel Does Not Teach or Suggest the Type of Expression Required by the '415 Patent Claims

The Examiner relies extensively on Axel to support his conclusions of obviousness. See Final Action at 12, 27-31. The conclusions the Examiner has drawn from Axel rest on a series of compounding factual errors. First, the Examiner asserts that the "Axel patent clearly possesses the concept of co-transforming a single eukaryotic or mammalian host cell to express functional proteins." Final Action at 28 (emphasis added). Then, after stating his incorrect belief that "co-transformation is synonymous with co-expression," the Examiner asserts that Axel suggests "co-transforming more than one desired gene for making proteinaceous materials which include multimeric proteins, such as interferon." Id. at 29. Building on these incorrect assumptions, the Examiner then incorrectly concludes that Axel is suggesting production of a "functional" antibody ("a 'functional' antigen- binding immunoglobulin molecule…") by "expressing two immunoglobulin chains in a single eukaryotic host cell, since Axel discloses and claims encoding an antibody that necessarily possesses both light and heavy immunoglobulin chains." Id. at 30. Finally, contrary to the direct testimony of three different expert witnesses in this case, the Examiner incorrectly asserts that "Axel discloses and claims the expression of antibodies in mammalian host cells as intact (assembled) proteins." Id. at 12-13. See also, Harris I ¶¶ 28-29; Harris II ¶ 47; Botchan ¶ 59; McKnight I ¶ 74; McKnight II ¶¶ 20-22.

Each of these conclusions of the Examiner is wrong. Together, they reveal that the Examiner reached his ultimate conclusions by reading into Axel hindsight "facts" needed to support his conclusions about Axel. An accurate and objective description of Axel shows that it describes nothing more than the conventional "one-at-a-time" strategy prevalent in April 1983 (i.e., the same conceptual approach embodied in the '567 claimed invention). And, contrary to the Examiner's beliefs, the extensive evidence (including the Axel disclosure) establishes that (i) Axel does not suggest, much less provide any guidance regarding how, to successfully transform a host cell with more than two DNA sequences; (ii) Axel failed to produce a host cell that successfully expressed anything other than a marker gene, (iii) Axel failed to produce and recover any functional proteins encoded by a DNA I sequence (the "desired" proteins), and (iv) Axel is entirely silent about producing an "intact (assembled)" antibody.

I. Axel Proposes the Same "One Polypeptide in a Host Cell" Strategy Shared by the '567 Claims

Axel proposes a conceptual strategy for attempting to produce a single eukaryotic polypeptide of interest. See Harris I ¶¶ 22-25, Harris II ¶ 38; Botchan ¶¶ 50, 51; McKnight I ¶¶ 69 -71; McKnight II ¶¶ 20-23. The Axel process employs two DNA sequences: a "DNA I" that encodes the polypeptide of interest (i.e., which is to be isolated from the cell after its production), and a "DNA II" that encodes a selectable marker that is not isolated from the cell. See Axel abstract. A person of ordinary skill in the art in April 1983 would have read Axel as being entirely consistent with the prevailing mindset of producing only one desired polypeptide at a time in a host cell. See McKnight II ¶¶ 8-16, 27; McKnight I ¶ 71; Harris II ¶ 44; Botchan ¶ 50.

Axel suggests that its disclosed "DNA I + DNA II" process may be suitable for producing a wide variety of types of eukaryotic polypeptides. See, e.g., Axel at col. 3, lns. 31-36. To this end, Axel includes a laundry list of proteins that had potential commercial significance at the time the Axel patent was written. As Dr. Harris explains:

> [T]he reference [in Axel] to "interferon protein, insulin, growth hormones clotting factors, viral antigens, antibodies and certain enzymes" would have been viewed by a person of ordinary skill in the art as simply being a laundry list of types of proteins having economic value at the time the Axel patent was filed. I believe a person of ordinary skill would view these and other references throughout the patent to "antibodies" as simply identifying an antibody polypeptide (i.e., a heavy or a light chain polypeptide) as a type of polypeptide that can be produced by the Axel process.

Harris II ¶ 42. In other words, all that Axel's laundry list would have told a person of ordinary skill in April 1983 is that the Axel procedure may prove suitable for producing these types of proteins using the "DNA I + DNA II" method, which, of course, is designed to produce only one of these polypeptides at a time in a recombinant host cell. See, e.g., McKnight I ¶¶ 67, 73-74; McKnight II ¶¶ 26-27; Botchan ¶¶ 49, 55, 60; Harris II ¶¶ 41-47; Harris I ¶¶ 21-30.

Contrary to the Examiner's beliefs, the mere inclusion of a laundry list of proteins does not provide any specific guidance about how to make any of these particular proteins, especially "antibodies." Dr. McKnight pointed out, for example, that:

> ... a well known enzyme in early April of 1983, RNA polymerase, has ten discrete subunits. Under the PTO's logic, the Axel patent is describing how to express all ten subunits of RNA polymerase in one host cell because RNA polymerase is an enzyme, and enzymes are listed in the patent specification and claims.

McKnight I ¶ 68. Instead, based on their careful analyses of the Axel disclosure, the experts concluded that Axel provides no guidance at all about producing multimeric protein structures such as antibodies. McKnight I ¶¶ 65-69, 71; McKnight II ¶¶ 26-27, Harris I ¶¶ 27, 28; Harris II ¶¶ 42-48; Botchan ¶¶ 50-53. As Dr. McKnight explains, if a person of ordinary skill in the art wanted to use the Axel technique to produce an immunoglobulin multimer in April 1983, that person would have read the Axel patent as teaching that he or she should:

> ... produce only one antibody polypeptide at a time using a host cell co-transformed with a marker gene and a DNA I sequence encoding the desired antibody polypeptide (i.e., produce one co-transformed host cell with a DNA I encoding the antibody heavy chain, and a different co-transformed host cell with a DNA I encoding the antibody light chain).

McKnight II ¶ 27. This approach, as Dr. McKnight explained, would have been the only one consistent with the "DNA I + DNA II" procedures described in Axel. See McKnight II ¶¶ 21-23, 26-27.

The experts who analyzed Axel point to numerous aspects within its disclosure which reinforce, rather than depart from, the prevailing "one polypeptide in a host cell" mindset in April 1983. See McKnight II ¶¶ 8-16, 27; McKnight I ¶ 71; Harris II ¶ 44; Botchan ¶ 50. For example, the experts explained that there is an extensive discussion in Axel of how to increase the odds of successful transformation of a "two DNA" experimental model (i.e., the disclosed DNA I + DNA II design). See McKnight II note 19, ¶ 29; McKnight I ¶ 73; Harris II ¶¶ 45-46; Botchan ¶ 60. The experts found no corresponding discussion of experimental designs that might have been suitable for introducing and expressing more than two DNA sequences in one host cell, or engineering a host cell to produce two or more desired polypeptides. See Axel at col. 4, lines 61-66 and col. 7, lines 3-9, discussing whether DNA I and DNA II should be "linked" or "unlinked" and col. 5, lines 45-50 discussing varying the ratio of copies of DNA I to DNA II. See Botchan ¶¶ 52-53; McKnight II ¶ 25. Coupled with its 1980 filing date, experts have explained that the lack of any guidance on how to adapt the disclosed Axel method to

introduce and express a third or fourth gene is telling – this type of experiment was simply not contemplated or suggested by Axel. See Botchan ¶ 53; McKnight II ¶ 25.

Dr. McKnight also pointed out that following the preferred method that Axel identifies for obtaining "DNA I" sequences would lead the person of ordinary skill to produce DNA I sequences that encode only one immunoglobulin polypeptide (i.e., a heavy or a light chain). In particular, he pointed out that the heavy and light chain genes reside on different chromosomes, and that using the restriction endonuclease technique disclosed in Axel for obtaining desired DNA I sequences would result in DNA I sequences that only encode one immunoglobulin polypeptide. McKnight II ¶ 26. When these DNA I sequences are used in the Axel "DNA I + DNA II" process, the resulting host cell will have been engineered to produce only one immunoglobulin polypeptide, not two as required by the '415 claims.

The evidence of record thus demonstrates that Axel describes nothing more than what is inherently required by the '567 patent – production of one desired polypeptide (e.g., a heavy or a light immunoglobulin chain polypeptide) in one transformed host cell. See Harris II ¶¶ 39, 44, 48; McKnight I ¶¶ 69-71; McKnight II ¶¶ 26-27; Botchan ¶¶ 50-54. And, as the Axel disclosure itself points out, Axel actually failed to show any success in executing its proposed strategy.

II. Axel Produced No "Functional" Desired Polypeptides

The Examiner relies on his belief that Axel describes production of "functional" proteins to conclude that Axel is "particularly suited" to producing immunoglobulin multimers through "co-expression" – which the Examiner incorrectly states is "synonymous" with "co-transformation." Final Action at 29. See supra at (d)(3)(B). The Examiner's reading of and conclusions drawn from Axel are simply incorrect. As Dr. McKnight explained:

> The Axel patent does not show production of any "functional" protein encoded by DNA I, much less a functional multimeric protein. Instead, it reports experimental results showing that the two attempts to express a "DNA I" sequence (i.e., a gene encoding a "desired polypeptide") in a co-transformed cell both failed. In both experiments, the Axel patent reports that host cells were successfully "co-transformed" with the "DNA I" sequence and the marker gene, but that the polypeptide encoded by the DNA I sequence was not produced in these co-transformed host cells.

McKnight II ¶ 21 (footnotes omitted). Dr. McKnight also explained that the Axel patent itself explains that the lack of production of any DNA I polypeptide was because the "co-transformed" cells failed to properly transcribe the DNA I sequence. See McKnight II ¶¶ 21-23.

To support his incorrect conclusion about "functional" proteins, the Examiner cites column 2, lines 34-36 of Axel. See Final Action at 30. However, as Dr. McKnight explained, this passage in Axel is actually discussing production of the selectable marker protein encoded by DNA II, and not the protein of interest encoded by the DNA I sequence. See McKnight II ¶ 20. Dr. McKnight also points out that Axel did not isolate or characterize the selectable marker protein, but instead inferred that it was functional because the cells gained resistance to the selection agent. Id.

Moreover, unlike the present Examiner, when the Office examined the sufficiency of the Axel disclosure relative to its then-pending claims for producing "functional" proteins encoded by DNA I sequences, it recognized these shortcomings and repeatedly rejected these Axel claims. In response to these enablement rejections, the Axel applicants canceled claims "directed to the production of protein from DNA I" (see, e.g., Patent Application No. 06/124,513 (Axel), Paper No. 4, Office Action mailed July 14, 1981 [App. B1762-B1773] at ¶ 8, Paper No. 9, Office Action mailed February 8, 1982 [App. B1774-1778] at ¶ 12, and Paper No. 15, Reply filed January 12, 1983 [App. B1791-1797] (canceling claims "directed to the production of proteins from DNA I"). As the Axel applicants stated then, they "canceled claims directed to production of protein from DNA I" "in a sincere effort to place [the] application in condition for allowance." Patent Application No. 06/124,513 (Axel), Paper No. 15, Reply filed January 12, 1983 at 6. In addition, when the Axel Examiner finally allowed the '216 patent, she revised the abstract to delete all references to production of "proteinaceous materials" including in particular the list of examples that includes "antibodies." Patent Application No. 06/124,513 (Axel), Paper No. 18, Examiner's Amendment mailed July 5, 1983, [App. B1798-1799].[17]

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[17] Claim 23 of Axel is directed to a process for producing "interferon protein, insulin, growth hormone, clotting factor, viral antigen or antibody." In connection with their amendment, the Axel applicants represented to the Office that: "[a]s so amended, claim 35 [patent claim 22] and 71 [patent claim 51] and the claims dependent thereon, 36-37 [patent claims 23-24] and 72-73 [patent claims 52-53], respectively, do not require that the protein which is produced

The data in Axel, and its prosecution history, thus show that the Axel does not describe enabling procedures for producing even one, functional desired polypeptide, much less a functional multimeric protein by producing two or more different desired eukaryotic polypeptides in a single transformed host cell.

III. Axel Did Not Show Successful "Co-Expression" of Two Foreign DNA Sequences

Another critical error made by the Examiner is his conclusion that Axel suggests "co-transforming more than one desired gene for making proteinaceous materials which include multimeric proteins, such as interferon." See Final Action at 29. This belief rests on a series of significant errors about what Axel is describing.

First, the Examiner improperly equates the experimental design of Axel – where one DNA sequence encodes a desired polypeptide, and the other encodes the selectable marker – with the experimental design that would be needed to genetically engineer a host cell to independently express two desired polypeptides. The experts explained this was improper because the "DNA I + DNA II" process of Axel requires that the DNA II sequence encode a selectable marker, and cannot encode a second "desired" polypeptide. For example, Dr. Harris explained:

> For the process described in the Axel patent to work, DNA II must encode a polypeptide that introduces a selectable phenotype not normally exhibited by the cell. A gene encoding an immunoglobulin heavy or light chain polypeptide cannot function in the role described in the Axel patent for DNA II, because its expression in a cell would not have introduced a "selectable marker" into the cell.

Harris I ¶ 24; Harris II ¶ 38; McKnight I ¶ 66; McKnight II ¶¶ 19-20. Several experts explained that the Axel "DNA I + DNA II" process would have been rendered inoperative for its intended purpose if one were to do as the Examiner suggests, and use a DNA II that encoded a second "desired" polypeptide, instead of a marker gene. Harris I ¶22-25; Botchan ¶ 48-50. As the court found in In re Schulpen, when modifications to prior art would render that prior art teaching

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be encoded by DNA I. Thus, claims 35-37 [22-24] and 71-73 [51-53] as amended cover production and recovery of thymidine kinase which, as the Examiner acknowledged in the Official Action, is disclosed." Patent Application No. 06/124,513 (Axel) [App. B1651-1761], Paper No. 12, Reply filed June 7, 1982, [App. B1779-1790] at 6.

inoperative for its intended purpose, the idea of making such modification "run[s] counter to its teachings" and helps demonstrate that a claimed invention that requires such modification is not obvious. In re Schulpen, 390 F.2d 1009, 1013, 157 U.S.P.Q. 52, 55 (C.C.P.A. 1968) (finding that "[r]ather than being made obvious by the reference, such modification would run counter to its teaching by rendering the apparatus inoperative to produce the disclosed [invention]."). See also In Re Gordon, 733 F.2d 900, 902, 221, U.S.P.Q. 1125, 1127 (Fed. Cir. 1984) (finding that because a modification should not be considered "obvious unless the prior art suggested the desirability of the modification", the fact that such a modification would render the prior art "inoperable for its intended purpose" argues against a finding of obviousness.)

Second, the Examiner's belief that Axel teaches successful "co-expression" of two DNA sequences in one host cell rests on his incorrect assumption that "cotransformation is synonymous with coexpression." Final Action at 29. Cotransformation according to Axel refers to the step of introducing foreign DNA into a host cell. See Axel, col. 4, lns 22-24. Expression, by contrast, refers to events that occur after the foreign DNA is in the host cell, and refers to the transcription of a gene (resulting in formation of mRNA) and translation of the mRNA (i.e., to yield a polypeptide having the amino acid sequence encoded by the DNA). See Axel, col. 4, lns. 55-60; see also McKnight II ¶¶ 17-29. As explained earlier, Axel itself disproves the Examiner's conclusion, by reporting that host cells successfully "co-transformed" with two DNA sequences (i.e., DNA I encoding the desired polypeptide and DNA II encoding the selectable marker) did not successfully express both DNA sequences. See McKnight II ¶¶ 21-23. Axel reports that while the marker gene (DNA II) was apparently expressed – based on the observation that the cell's phenotype changed to acquire resistance to the selection agent – the DNA I sequence (encoding the desired polypeptide) was not. See McKnight II ¶¶ 21-23.

Third, the Examiner relies on Axel's disclosure of "interferon protein" to support his incorrect conclusion that Axel is describing procedures for producing functional desired multimeric proteins. Final Action at 29-30. The interferon proteins in the Axel disclosure are not multimeric, but instead consist of a single polypeptide chain. See McKnight II ¶ 21 (footnote 14). In addition, glycosylation of a protein involves putting sugar residues on a polypeptide chain, and is not related to forming multimeric protein complex.

Fourth, the Examiner's argument that "preferred proteinaceous materials include multimeric proteins … in which the Axel method is advantageously employed" finds no literal or inferential basis in the actual disclosure in Axel. Final Action at 30. Instead, the proteins that were employed in the examples in Axel were all small, simple, monomeric polypeptides. (e.g., ß-globin, a ~16 kD single polypeptide). See Harris II ¶ 39. Dr. Harris also explained that there is no discussion anywhere in Axel that is directed to the topic of producing multimeric proteins, much less production of a large (~150 kD), complex immunoglobulin multimer. Harris II ¶ 39; McKnight I ¶¶ 65, 69, 71, 77; McKnight II ¶¶ 21, 69-71.

Accordingly, the Examiner's conclusions about what Axel teaches and what it would have suggested to a person of ordinary skill in the art in April 1983 are contradicted by the actual disclosure in Axel and by numerous expert declarations. See, e.g., McKnight II ¶¶ 20-23; Botchan ¶¶ 50-51; McKnight I ¶¶ 69-71; Harris I ¶¶ 25, 29-30; Harris II ¶ 38. His fundamental errors about what is described in Axel directly affect his ultimate conclusions regarding Axel (i.e., that it reports production of "functional" antibodies by "co-expression" procedures). What Axel actually reports is a complete failure to achieve successful expression of even one DNA I sequence, much less production and recovery of "functional" desired polypeptides encoded by DNA I sequences. See McKnight II ¶ 21. Consequently, a person of ordinary skill in the art would not have read Axel as showing or suggesting that one could predictably achieve co-expression of two different DNA sequences in a single host cell, simply by demonstrating that the cell had been successfully "co-transformed" with these two sequences. See, e.g., McKnight II ¶¶ 23-29; Botchan ¶¶ 56, 62; McKnight I ¶¶ 76-77; Harris I ¶ 30.

IV. Axel Does Not Teach or Suggest Expressing Multiple DNA Sequences Encoding Different "Desired" Polypeptides in One Host Cell

To support his belief that Axel teaches production of multiple desired polypeptides in one host cell, the Examiner points to references in the Axel abstract referring to the use of "genes." See Final Action at 29-31. The Examiner asserts that this proves that Axel is describing procedures where multiple DNA I sequences encoding multiple different desired polypeptides are being inserted into and expressed by a single host cell. See id. The Examiner is incorrect.

The use of the plural word "genes" in the Axel abstract (Final Action at 29) does not show that Axel is describing procedures for inserting different "DNA I" sequences into a host cell, as asserted by the Examiner, but is instead referring to the concept of inserting multiple copies of the same DNA I sequence into a eukaryotic cell to increase the number of copies of that DNA I sequence in that cell. See Harris II ¶¶ 45-46. Indeed, three different experts explained that the use of the term "genes" generally refers to strategies disclosed in Axel for inserting extra copies of the same DNA I sequence relative to the number of copies of the DNA II sequence in the transformed host cell. See, e.g., Harris II ¶¶ 45-46; McKnight I ¶ 73; Botchan ¶ 60; McKnight II ¶ 29. The experts also explained that these references to "genes" in the Axel abstract would not have overridden the explicit and clear description throughout Axel that its "DNA I + DNA II" process is a strategy for engineering a host cell to produce only one desired polypeptide. See id. These experts explained that the entirety of Axel is devoted to the DNA I + DNA II experimental design, and that there is no discussion whatsoever of the idea of expressing additional DNA sequences beyond the DNA I and DNA II sequences. See, e.g., Harris I ¶ 25; Harris II ¶ 38; McKnight I ¶ 69; Botchan ¶ 60; McKnight II ¶¶ 24-26, 29.

V. Axel Does Not Show or Suggest Production of "Intact (Assembled)" Antibodies by Producing Heavy and Light Immunoglobulin Chains in One Host Cell

Another significant error made by the Examiner is his conclusion that "Axel discloses and claims the expression of antibodies in mammalian host cells as intact (assembled) proteins." Final Action at 12-13. The Examiner maintains this belief despite the fact that three different experts directly stated that there is no description or suggestion in Axel of anything that addresses the question of assembly of an antibody multimer, much less an express or implicit teaching of production of "intact (assembled)" antibodies.

The Examiner tries to support his conclusions in three different ways.

First, the Examiner tries to read the idea of producing heavy and light antibody chains in a single host cell into the word "antibody" as it appears in the Axel patent. In the Final Action, for example, the Examiner asserts that the "ordinary meaning" of antibody is a tetrameric protein, and that this, somehow, supports his belief that Axel suggests producing heavy and light chains together in a single host cell, rather than the more general idea of using the Axel DNA I

(desired protein) + DNA II (marker) method to produce an antibody. Final Action at 28, 30. The Examiner is again incorrect.

As explained above, the inclusion of "antibody" in a laundry list of types of proteins would not have conveyed to a person of ordinary skill in the art anything about how a multimeric antibody structure might be produced using the Axel DNA I + DNA II technique. Instead, the way the term is used in the specification suggests that the Axel inventors viewed an antibody polypeptide as being just one type of polypeptide that conceivably could be produced using the Axel DNA I + DNA II process. See, e.g., McKnight I ¶¶ 67, 73-74; McKnight II ¶¶ 26-27; Botchan ¶¶ 49, 55, 60; Harris II ¶¶ 41-47; Harris I ¶¶ 21-30. And, simply writing the word "antibody" in the Axel patent specification plainly would not be enough to advance the field beyond what was known from the experimental data at that time. See, e.g., Botchan ¶ 61 (in discussing declaration from Dr. Axel (Declaration of Dr. Axel, [App. B1397-B1405]),, observing that it "is clear to me that Dr. Axel attributes the guidance needed to extend the procedures in the Axel patent to make a recombinant antibody or antibody fragment through coexpression to the information in the '415 patent.") See also McKnight I ¶ 72.

Second, the Examiner asserts that "the selection of an antibody as one or more (multiplicity) of the foreign protein(s) encoded by DNA I is a patented embodiment" and then states that the Axel claims are "presumed valid under 35 U.S.C. § 282 unless invalidated by 'clear and convincing evidence' and additionally references are presumed to be operable and enabled." Final Action at 28. Presumably, the Examiner makes these references to the presumption of validity in an attempt to shield his scientifically incorrect interpretation of what Axel describes. None of these legal doctrines is implicated here, because there is no need to "invalidate" the Axel claims in order to find that Axel does not describe production of "an assembled (intact) antibody" as the Examiner asserts. For example, there is no requirement in the Axel claims that the antibody be produced by independently expressing DNA sequences encoding antibody heavy and light chain polypeptides in a single host cell. Instead, the claims simply recite processes of transforming eukaryotic host cells using a DNA I sequence that encodes an antibody polypeptide. Even if the Axel claims could somehow be construed as requiring production of an antibody multimer, nothing in the Axel claims requires that this

antibody multimer be produced using heavy and light chain polypeptides made in the same host cell. See, e.g., McKnight II ¶27; Harris II ¶47.[18]

The Examiner also ignores the fact that the Axel claims at issue (claims 7, 23, 29, 37, and 60) are each dependent upon a parent claim that specifies use of a DNA I sequence that encodes a single polypeptide. This results from the claims' use of the term "proteinaceous material" which is defined at col. 4, lns. 28-29 of Axel as being a "biopolymer formed from amino acids" rather than the more general concept of a protein that might include multimeric structures. As Dr. McKnight explains, a "biopolymer" is a single polypeptide consisting of a sequence of amino acid residues linked by peptide bonds, not a multimeric protein complex made up of different polypeptides associated through non-covalent interactions or disulfide bonds. McKnight II at note 12.

Third, the Examiner attempts to use evidence of licensing of the Axel patent, reported in a law review article[19], to support his opinion that Axel describes and enables production of "functional proteins, including antibodies." Final Action at 46. However, as Dr. Walton's declaration explains, evidence of licensing of the Axel patent does not support this conclusion. See Walton ¶¶ 10-20. Instead, to the extent that this licensing evidence shows anything, it is that the industry recognized the Axel patent as being directed to a technique of introducing a specific type of selectable marker into mammalian host cells to permit identification of successfully transformed host cells. See Walton ¶¶ 10, 16-17.

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[18] The only interpretation of the Axel claims that must be ruled out by operation of the presumption of validity under § 282 is one that requires production of an "intact (assembled) antibody" using heavy and light chains produced in a single transformed host cell, as only this possible interpretation would render the Axel "antibody" claims invalid under 35 U.S.C. § 112, first paragraph, in view of the clear and convincing evidence of record showing that such a process has no support in the Axel description. See, e.g., Phillips v. AWH Corp., 415 F.3d 1303, 1327, 75 U.S.P.Q.2d 1321, 1337 (Fed. Cir. 2005) (en banc) (observing maxim that court should resolve ambiguities it perceives to exist in a claim in a manner that would support validity).

[19] Harvard J. L. & Tech. 17(2):583-618 (Spring 2004), "Recent Developments," [App. B1429-1464].

D. Rice Expressed a Single Recombinant Light Chain Gene and Reported Unpredictable Results

The Examiner relies extensively on Rice to support the rejections. In particular, he asserts that "Rice demonstrates the successful expression of both heavy and light chains in a host with subsequent assembly into immunoglobulins." Final Action at 13. The Examiner's determination of what Rice describes, and what it would have conveyed to a person of ordinary skill in the art in April 1983 is directly contradicted by the testimony of several experts, including the first author of the paper, Dr. Douglas Rice.

I. Rice Does Not Describe or Suggest the '415 Claimed Invention

Rice teaches nothing more than the transformation of, and expression in, a mutant lymphoid cell line – the 81A-2 cell line – of a single foreign immunoglobulin light chain gene. See McKnight II ¶ 30; McKnight I ¶¶ 79-91; Rice I ¶¶ 9-10, 12-13; Rice II ¶¶ 28-30; Botchan ¶¶ 63-72; Harris I ¶¶ 31-39; Harris II ¶¶ 52-67. The extensive evidence of record contradicts the Examiner's conclusion that one of ordinary skill would have concluded that the experimental results found in Rice would have made producing a transformed host cell that independently expresses DNA sequences encoding foreign heavy and foreign light immunoglobulin polypeptides predictable in April 1983. See, e.g., McKnight II ¶¶ 34-37; Rice I ¶¶ 14-15; Rice II ¶¶ 13-16, 30-32; McKnight I ¶¶ 79-91; Botchan ¶¶ 63-72; Harris I ¶¶ 31-39; Harris II ¶¶ 51-53, 57-60, 63.

In April 1983, it was known that naturally occurring B-cells were unique cells, and the only ones in nature that produced antibodies. It was also known that naturally occurring B-cells mediated the rearrangement and expression of immunoglobulin genes, and the assembly and secretion of immunoglobulin molecules. This gene rearrangement capacity – unseen in any other type of cell in April 1983 – provides the B-cell with its ability to generate the incredible diversity of antigen binding specificity observed in nature.

The unique attributes of B cells, and the desire to better understand their behavior, led to a tremendous amount of research into B-cells by prominent scientists. One team of those researchers, led by Drs. David Baltimore and Douglas Rice, focused their research on the mechanisms in the B-cell that regulated immunoglobulin gene expression. In 1982, they

published the Rice paper cited by the Examiner. As Drs. Baltimore and Rice observed in that paper,

> Although much is now known about Ig gene structure, relatively little is known about the molecular mechanisms that control Ig gene expression. One approach to study such controls is to introduce Ig genes into various cell lines, including both lymphoid cells at various stages of differentiation and nonlymphoid cells. One might then be able to identify control mechanisms unique to lymphoid cells that allow the cells to express, assemble, and secrete Igs.

Rice at p. 7862. See also Rice I ¶ 7; Rice II ¶¶ 9-16, 20-24; Botchan ¶¶ 68, 71; Harris I ¶¶ 32-33; McKnight I ¶¶ 81, 111.

As Dr. Rice has explained, the objective of the work he and Dr. Baltimore reported in their 1982 paper was "to develop an experimental platform for understanding the molecular mechanisms associated with the regulation of Ig gene expression." Rice I ¶ 7. The reasons why Drs. Rice and Baltimore conducted the experiments described in the Rice publication are directly relevant to understanding what this paper would have suggested to a person of ordinary skill in the art in April 1983. As he explained, "we were not attempting to develop a system for recombinantly producing immunoglobulins." Id.

Importantly, the particular experimental conditions used in Rice were tailored to the study of native immunoglobulin gene expression, and not to the production of a desired protein using genetic engineering. See Botchan ¶ 65, Harris II ¶ 57, McKnight II ¶ 30, Rice at 7862, col. 1, ¶ 2; Rice I ¶ 7. As Dr. Rice explained, the cell line they used in their experiments (the 81A-2 mutant) was chosen because it was "poised to express the foreign light chain gene." Rice I ¶ 10; Rice II ¶ 31. This cell line would have been seen, in April 1983, as being inappropriate to use to produce "fully recombinant" immunoglobulin multimers because it was expressing its endogenous heavy chain gene which would have "contaminated" a recombinant immunoglobulin product. Rice I ¶¶ 10-12; Rice II ¶ 31; see also Botchan ¶ 67.

Other publications investigating the behavior of cultured lymphocytes before April 1983 would have shaped the expectations of a person of ordinary skill in the art about the showings in Rice. See, e.g., Rice II ¶ 10 Those publications reported experimental results suggesting that the normal functions of B-cells (e.g., their ability to successfully express their endogenous

immunoglobulin genes, produce heavy and light chains, assemble and secrete antibodies, and even remain viable in culture) was dependent on many interrelated factors including the stage of development of the B-cell, the timing and levels of expression of the endogenous heavy and light chain genes in the B- cell, and the presence of "helper" proteins in the cell and other factors. See, e.g., Rice II ¶ 16, McKnight I ¶¶ 86, 104; Colman ¶¶ 31-32; Harris II ¶¶ 22-27; Botchan ¶ 68. These publications also reported experimental results showing disruption of the ability of a naturally produced B-cell to express its genes and secrete immunoglobulin multimers. For example, certain publications reported examples of cultured lymphocyte cells that had lost their ability to express one or both of their endogenous genes, to properly produce endogenous heavy and light chains, or to assemble and secrete immunoglobulin multimers. Rice II ¶¶ 13-14. Other publications reported that excessive or unbalanced production of heavy and light chain polypeptides actually could cause cells to die (a phenomenon termed "heavy chain toxicity"). See, e.g., Colman ¶ 31; Botchan ¶ 71; Harris II ¶ 25; McKnight I ¶ 90, 104; Rice II ¶ 14.

Rice itself suggests that "the possibility that transcription of the light chain gene is controlled by a product of the heavy chain locus is an interesting possibility and needs further investigation." Rice at 7865; see also, e.g., Rice II ¶ 20, Harris II ¶¶ 27-28, 54-55; McKnight I ¶¶ 85-86. A person of ordinary skill would have read this observation in Rice as indicating the authors' belief that the continued expression of the endogenous heavy chain gene in the 81A-2 cell line was necessary to achieve expression of the single foreign light chain gene they introduced into the cell. Thus, the information actually reported in Rice would have led a person of ordinary skill in the art to doubt that Rice's mature lymphocyte cell line could be transformed with an additional heavy chain gene without substantially disrupting one or more of these interrelated functions. Rice II ¶¶ 13, 16; Botchan ¶¶ 66-72. As Dr. McKnight concluded, Rice

> would not have led a person of ordinary skill in the art to expect that a B cell would express two exogenous genes and that the expression products of these two genes 'in a competent host would result in the assembly of a functional antibody.' There is simply no foundation for this within the Rice paper, or in the literature in that time period relating to immunoglobulin gene expression. (emphasis added).

McKnight I ¶ 87. See also Harris II ¶¶ 62-63.

Despite this evidence, the Examiner somehow credits Rice with conveying to a person of ordinary skill in April 1983 a "reasonable expectation" that any lymphocyte cell could be

transformed with a foreign heavy and a foreign light chain gene, that it would properly express both genes, produce the light and heavy chains, assemble the chains into an immunoglobulin multimer and secrete that multimer from the cell, all while remaining viable. To reach this conclusion, the Examiner must ignore or completely fail to understand the actual observations contained within Rice, and the experts' explanation of their significance. Rice, alone or together with the other cited references, would not have led a person to extrapolate the limited experimental results reported in it to reach the hypothetical transformed lymphocyte cell upon which the Examiner's conclusions are based.

Similarly, the Examiner has somehow found within Rice "ample motivation to clone both light and heavy chains into an analogous competent eukaryotic host cell with a reasonable expectation of success." Final Action at 31. This perceived motivation exists solely in the mind of the Examiner, as it is not found in the reference itself, which reports unpredictable results even as to expression of a single foreign light chain gene. See, e.g., McKnight II ¶ 33; Rice I ¶ 14. In particular, it ignores the significance of the Rice observation that transcription of a single foreign light chain gene was believed to be under the control of a product of the heavy chain locus (Rice at 7865, last paragraph; McKnight I ¶ 83), which would have led the person of ordinary skill in the art to not take steps – such as introducing another foreign heavy chain gene into the cell –that might affect the continued, normal expression of the cell's endogenous heavy chain gene.[20]

II. The Examiner Improperly Equates the '415 Claimed Invention to the Actual Rice Experiments

The Examiner's conclusions about Rice rest on a fundamental error. Specifically, the Examiner has incorrectly characterized the continued expression by Rice's transformed 81A-2 cell line of its endogenous (native) heavy chain gene as an "expression" equivalent to the expression in that cell of a foreign DNA sequence encoding a foreign heavy chain polypeptide. In particular, the Examiner states his belief that Rice showed "successful expression of both heavy and light chains in a host cell with subsequent assembly into immunoglobulins," and then relies upon this mistaken belief to conclude that a person of ordinary skill in the art, in April

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[20] This is particularly relevant to the nonobviousness of claims 17 and 18 directed to transformed host cells comprising at least both the variable domain of the light and heavy chain genes.

1983, would have expected the same thing to occur in a lymphocyte that had been transformed with two different foreign immunoglobulin genes. Final Action at 33, 36-38.

The experts explained that this extrapolation by the Examiner is scientifically unjustified. For example, as Dr. McKnight stated:

> A scientist working in this field would not equate a cell's expression of its own endogenous genes [with] the introduction and expression of a foreign DNA sequence in that organism. If this were the case, genetic engineering would have been a trivial task. Thirty years of experience demonstrates the contrary.

McKnight I ¶ 82. See also Rice II ¶¶ 27-28 ("The PTO fails to make a critical distinction between the normal continued expression of an endogenous heavy chain gene by this cell line and the introduction and "successful expression" of the functionally rearranged exogenous light chain gene that was described in the paper."); Harris II ¶¶ 61-62; Botchan ¶¶ 67, 68; McKnight I ¶¶ 86-87; McKnight II ¶¶ 34-36.

The evidence instead shows that, in April 1983, a person of ordinary skill in the art would not have equated the Rice showing of successful "expression" of its endogenous (native) heavy chain gene and expression of a single foreign light chain gene, with what might happen in a lymphoid cell line if two different foreign immunoglobulin genes were introduced into the cell. Harris I ¶¶ 32, 36-37; McKnight I ¶¶ 81-82, 85-87; Harris II ¶¶ 59-62.

Indeed, Rice itself reports that the processes governing expression of its single foreign immunoglobulin gene in a lymphoid cell following the procedures in Rice were not well understood and regulated by unknown and uncharacterized factors. See, e.g., Harris II ¶¶ 57-59; Botchan ¶ 72; McKnight I ¶¶ 83-87, 91.

III. The Examiner Improperly Dismissed the Relevant Testimony of Qualified Experts

The Examiner either completely ignores -- or dismisses for a variety of unjustified reasons -- the §1.132 evidence concerning Rice. For example, the Examiner found unpersuasive the testimony of Drs. Botchan, Harris and Rice on the significance of the unpredictability reported in Rice and its relevance to the '415 claimed invention because:

> Knowledge of mechanism (e.g., the factors that regulate gene expression) is not always complete or even known prior to practicing a claimed invention. Additionally, with respect to uncertain variables including uncharacterized control elements or possible influence by continued heavy chain expression discussed in the Rice and Baltimore article, it is noted that scientific experimentation always involves unknown parameters(s).

Final Action at 31.

Certainly, the failure of a prior art reference to reveal how or why a particular result has been achieved is not fatal to the teaching value of that reference as to the results that were actually reported. That maxim, however, is entirely inapplicable in the present case. This is because the experiments upon which the Examiner has based his conclusion were not actually described in Rice. Instead, the Examiner has based his opinions and conclusions on a hypothetical experiment with a lymphocyte cell not discussed or suggested anywhere in Rice. See McKnight I ¶ 90.

In this instance, the absence of any discussion in Rice of an experiment analogous to the '415 claimed invention, coupled with the absence of explanations in Rice for the unpredictable results they reported about the simpler experiments they actually performed, is fatal to the Examiner's asserted "teaching" value of Rice in April 1983. As the experts pointed out, Drs. Rice and Baltimore, after acknowledging that the mechanisms that governed control of expression of immunoglobulin genes were "poorly understood," plainly state in their paper that further research would be needed to understand why they observed the results they did. See, e.g., Botchan ¶¶ 68-72, McKnight I ¶¶ 83-85. As Dr. Botchan concluded, "the Rice paper raises more questions than it answers concerning the transcriptional regulation of the exogenous light chain gene." Botchan ¶ 66.

Despite the evidence, and without citing anything to support his contrary views, the Examiner states "it was well within the skill of the art to obtain appropriate coding sequences for both antibody chains and transform a competent eukaryotic host cell." Final Action at 31. As Dr. Botchan states:

> In my opinion, the PTO's views are inconsistent with the views of a person of ordinary skill in the art in early April of 1983. In fact, I believe they are inconsistent with the views of the authors of the Rice paper. For example, the

> authors observed that uncharacterized or novel mechanisms in the transformants regulated the expression of the light chain gene they introduced. The logical implication of this observation is that a person of ordinary skill in the art would have concluded that those regulatory mechanisms should be deciphered and understood before attempting to extend the experimental model (e.g., by attempting to express another exogenous immunoglobulin gene).

Botchan ¶ 69. The Examiner's unsupported assertions are at odds with the evidence of record, and cannot take the place of proper fact-finding.

The Examiner concludes that the "Rice and Baltimore teaching of successfully cloning a light chain into a heavy chain producing B lymphocyte that secretes assembled antibody would provide ample motivation to clone both light and heavy chains into an analogous competent eukaryotic host cell with a reasonable expectation of success." (emphasis added). Final Action at 31; see also id. at 33. These conclusions rest on serious factual errors the Examiner makes in reading Rice.

For example, the Examiner ignores the fact that in the experiments reported in Rice, the expression products made by the transformed cell were not secreted. Instead, the transformed cells were lysed (i.e., broken apart), their contents released into the cell culture medium, and then the expression products detected by running the crudely purified cell extracts on a polyacrylamide gel. See Rice at 7863 (Fig. 2) (reporting results using "extracts" of the transformed cells). Dr. Rice explained that they did not undertake to recover, purify or otherwise characterize these expression products. Rice I ¶ 16. In addition, as explained above, the Examiner's conclusions about the "reasonable expectations of a person of ordinary skill in the art" are directly at odds with the well-reasoned opinions of experts who explained, through citations to contemporaneous publications, how such a person would have read Rice in April 1983.

The Examiner also improperly dismisses the expert testimony that explains why a person of ordinary skill in the art, after considering information in the scientific literature before April 1983, would not have extrapolated Rice in the manner the Examiner asserts. The Examiner first attempts to respond to this evidence using a legally flawed, and often simply illogical line of reasoning. For example, the Examiner dismisses the reports of toxicity associated with excess heavy chain production in hybridomas because, in his opinion, this phenomenon does not occur

in "normal" B-lymphocytes, and "lethality occurring from excess heavy chain expression is not the norm but the exception." Final Action at 36. In reaching these conclusions, the Examiner ignores testimony of three different experts who explained that Rice, Ochi and Oi (i) would not have led a person of ordinary skill to expect to see "normal" lymphocyte behavior in a lymphocyte host cell that has been transformed with multiple foreign immunoglobulin genes, and (ii) all report significant fluctuations in the levels of expression of foreign light chain genes that were used to transform their respective lymphocyte cell lines. Rice II ¶¶ 30-32; Botchan ¶¶ 67-72; McKnight II ¶ 34.

The Examiner then asserts that this testimony is unpersuasive because it fails "to provide definitive evidence that precludes a reasonable expectation of extrapolating the Rice and Baltimore article's teaching of lymphocyte secretion of assemble antibody to co-expression of a compatible eukaryotic host." Final Action at 36-37. In other words, the Examiner believes that this expert testimony is entitled to no or little weight because it does not contain "definitive evidence" from pre-April 1983 publications proving that the Examiner's hypothetical extrapolation from the actual Rice experiments would not work. Under the Examiner's standard, virtually no evidence from a qualified expert would ever be "persuasive."

The Examiner has also simply ignored a substantial amount of the expert testimony provided in this case concerning Rice. The experts identified a number of publications published before April 1983 that had identified factors that would directly undermine the Examiner's conclusions based on his reading of Rice. Examples of points the experts made which the Examiner has not addressed include:

- the observation that how and when heavy and light chains genes are expressed in native B-cells can affect assembly of an immunoglobulin (Botchan ¶ 71 citing Wabl, Hass & Wabl, Hendershot, Kohler, and Wilde & Milstein),
- whether transcription of the light chain gene was controlled by the heavy chain locus (McKnight I ¶ 85),
- the prevailing belief that expression of immunoglobulin genes and assembly of immunoglobulins were linked events within B-cells (McKnight I ¶ 86 citing Valle, Roch & Koshland, Wabl & Steinberg),

- that successful production of immunoglobulins was highly dependent on the sequence of expression and levels at which the two immunoglobulin genes were expressed (McKnight I ¶ 104 citing Colman),
- that the levels of expression of each immunoglobulin gene could affect production of the other immunoglobulin polypeptide (McKnight I ¶ 104 citing Rice),
- the stage of development of the B-cell could affect immunoglobulin gene expression (McKnight I ¶ 104 citing Siden et al.), and
- the belief that helper proteins were necessary to enable a B-cell to assemble an immunoglobulin multimer, and that these helper proteins would not be found in other types of cells that might be used as host cells (McKnight I ¶104 citing Wabl & Steinberg).

The record shows that the Examiner gave this evidence essentially no consideration and certainly no weight. This is improper under established Office practice. M.P.E.P. § 716.01 et seq.

IV. The Examiner Improperly Relies on a Third-Party Declaration About a Hypothetical Experiment Not Disclosed or Suggested in Rice

The only evidence identified by the Examiner to support his opinions about Rice is a third party declaration of Dr. David Baltimore, [App. B1397-1404].[21] Final Action at 32-37. Specifically, the Examiner relies on one paragraph in Dr. Baltimore's declaration, which reads:

> We did not perform further experiments to demonstrate that two exogenous chains of a known antibody or one exogenous and one endogenous chain of a known antibody, if produced in the same mammalian cell, would assemble into a functional antibody. However, in light of our demonstration that an introduced light chain gene encoded a protein that would combine with an endogenous heavy chain, without further testing of this idea I and other [sic] working in the field would have expected that if two chains were expressed, they would form a functional antibody. (emphasis added).

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[21] As Owners pointed out, Dr. Baltimore was not a disinterested third party. Instead, he served as a Director of MedImmune, which, acting through a third party, requested ex parte reexamination of the '415 patent on December 23, 2005. In addition, at the time that Dr. Baltimore prepared his declaration, MedImmune was in active litigation with Genentech over the '415 patent. See Brief for Petitioners at 48, n.18, MedImmune, Inc. v. Genentech, Inc., No. 05-608 (S. Ct. filed May 15, 2006). Dr. Baltimore also did not disclose in his § 1.132 declaration his relationship to the third party requestor that provided his declaration with their request for ex parte reexamination, or his financial interest in and relationship to that third party requestor (i.e., MedImmune).

Baltimore Declaration ¶ 5. The Examiner's reliance on Dr. Baltimore's declaration to offset the reasoned testimony of qualified experts based on contemporaneous scientific publications is substantively unpersuasive and legally improper.

Initially, Dr. Baltimore, through his declaration, confirms Dr. Rice's recollections that neither he nor Dr. Rice ever attempted to produce a transformed lymphocyte that would express foreign heavy and foreign light chain genes before the '415 invention. Rice II ¶¶ 51-52; Rice I ¶¶ 12-13.

Dr. Rice also testified that neither he nor Dr. Baltimore ever attempted to conduct experiments that might indicate whether a multimeric immunoglobulin structure could be assembled by expressing in a single lymphocyte cell multiple foreign immunoglobulin genes. Rice II ¶¶ 50-51. See also Rice I ¶ 13 ("It never occurred to us, as part of our work leading to the results published ... [in Rice] ... to attempt to express exogenous heavy and light chain genes in the 81A-2 cell line."). And, Dr. Rice testified that, at the time he and Dr. Baltimore conducted their work that led to the Rice publication, Dr. Baltimore never expressed to him an opinion comparable to what Dr. Baltimore expressed in paragraph 5 of his declaration. Rice II ¶¶ 53-54. Thus, it is crystal clear that Dr. Baltimore is offering an opinion about a hypothetical experiment not described or discussed anywhere in the Rice paper (i.e., a lymphocyte cell line transformed with foreign heavy and foreign light chain genes). Rice II ¶ 58, McKnight II ¶ 35.

Dr. Baltimore also never suggests – either in his 1982 paper or in his 2007 Declaration – that he believes the hypothetical lymphocyte he bases his conclusions upon could have been predictably produced in April 1983. Instead, he expressly conditions his opinions on this critical point – "if two chains were expressed [by this hypothetical cell]." Dr. Baltimore's declaration thus operates to confirm the opinions of other experts in this proceeding who explained that a person of ordinary skill in April 1983 would not have believed this hypothetical transformed lymphocyte cell could have been predictably produced, and used to express heavy and light chains, in April 1983 based on the teachings in Rice and the other cited references. See Botchan ¶¶ 70-72; McKnight I ¶¶ 89-90. As Dr. McKnight observed, this would have been a big "if" in April 1983. See McKnight I ¶ 90.

Dr. Baltimore's opinion also does not address whether he or a person of ordinary skill in the art would have believed the '415 claimed invention as a whole could have been predictably achieved in April 1983. In other words, Dr. Baltimore has carefully segregated his opinion to address only one requirement of the '415 claims. Based on what it contains, Dr. Baltimore's opinion provides no insights of relevance to the question of whether a person of ordinary skill in the art would have believed the '415 claimed invention as a whole would have been obvious in April 1983 based on the '567 claims and the cited references. The Examiner had no reasonable basis for relying on it for this purpose.

The Examiner's reliance on the Baltimore declaration is also legally improper. First, the Baltimore declaration is not expressing any opinions that "explain . . . [the] printed publications in more detail." Instead, it is addressing a theoretical experiment not disclosed in or suggested by Rice (the only reference Dr. Baltimore discusses in his declaration). On this basis alone, it is improper for the Examiner to rely on Dr. Baltimore's declaration in this proceeding. (M.P.E.P. § 2258(I)(E)).

Second, Dr. Baltimore's declaration is not offering any opinions of a person of ordinary skill in the art. As paragraph 5 of his declaration makes clear, Dr. Baltimore is expressing his personal opinion (i.e., he states: "I and other [sic] working in the field would have expected ..."), and as of April 1983 Dr. Baltimore by any measure could not have been considered a person of "ordinary skill" in the art. By that time, he had already been awarded the Nobel prize, and had skills, training and experience far beyond those that would have been possessed by a person of ordinary skill. See Rice II ¶¶ 46-48. These extraordinary skills would have given Dr. Baltimore unique insights, perspectives and beliefs that would not have been shared by a person of ordinary skill.

The Examiner nonetheless reasons that despite this, Dr. Baltimore's personal opinions are entitled to significant weight because Dr. Baltimore has "at least" the level of education and experience that a person of ordinary skill in the art would have had. Final Action at 35. This is clear legal error. As the Federal Circuit explained in Envtl. Designs, Ltd. v. Union Oil Co. of Cal., 713 F.2d 693, 218 U.S.P.Q. 865 (Fed. Cir. 1983), someone with skills far above and beyond those of ordinary skill in the art cannot be considered one of ordinary skill in the art:

> The important consideration lies in the need to adhere to the statute, i.e., to hold that an invention would or would not have been obvious, as a whole, when it was made, to a person of "ordinary skill in the art"- not to the judge, or to a layman, or to those skilled in remote arts, or to geniuses in the art at hand.

713 F.2d at 697, 218 U.S.P.Q. at 868-69 (emphases added). See also Hybritech Inc. v. Abbott Labs., 4 U.S.P.Q.2d 1001, 1008-9 (C.D. Cal. 1987) (finding that "persons of superior skill, intellect and insight" who "were leading authorities" in the field did not qualify as persons of ordinary skill in the art); Studiengesellschaft Kohle mbH v. Dart Indus., Inc., 549 F. Supp. 716, 732, 216 U.S.P.Q. 381, 391 (D. Del. 1982) (holding that Nobel laureate's theorizing did not represent the application of "ordinary skill in the art of which said subject matter pertains").

The Examiner also defends his decision to give the Baltimore declaration equal weight to the testimony of the other experts by citing legal authority that provides that "[t]he weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains." (Final Action at 34, citing In re Buchner, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331 (Fed. Cir. 1991); M.P.E.P. §§ 2164.05, 2124). The Examiner portrays this legal authority accurately. Despite doing so, he somehow concluded it would be appropriate for him to accord the same weight to Dr. Baltimore's biased, speculative thought-piece about a theoretical experiment not reported in Rice as he gives the reasoned and factually supported opinions of qualified experts having contrary views. Under the legal authority the Examiner cites, it was clear legal error for the Examiner to give Dr. Baltimore's declaration any weight, much less equivalent weight. See, e.g., Rice II ¶¶ 9 - 32; Botchan ¶¶ 63-72.

E. Kaplan and Moore Direct the Person of Ordinary Skill Down a Different Path Than What is Required by the '415 Invention

The Examiner has managed to overlook the powerful message supporting the non-obviousness of the '415 claimed provided in two of the references he cites (i.e., Kaplan and Moore). That message is that a person of ordinary skill in the art wishing to produce an immunoglobulin multimer using recombinant DNA techniques in April 1983 should (i) produce the heavy and light chain polypeptides in separate host cells, as required by the '567 claims, and (ii) after recovering each chain from its separate host cell, assemble the immunoglobulin multimer by combining the individually produced chains in a test tube. McKnight II ¶¶ 8-16.

Indeed, Kaplan and Moore are the only two references the Examiner cites that explicitly discuss the production of multimeric immunoglobulin structures using genetic engineering techniques. Each reference clearly tells the person of ordinary skill to use a process that follows, rather than departs from, the '567 claimed approach of producing only one immunoglobulin polypeptide at a time in a host cell. Thus, Kaplan and Moore serve as evidence, particularly in combination with the '567 claims and the other cited references, that the '415 claimed approach of making immunoglobulin multimers would not have been considered obvious in April 1983 by a person of ordinary skill.

I. The "Road Map" in Kaplan Leads Away from the '415 Claimed Invention

Kaplan describes a plan for producing an immunoglobulin multimer where the individual heavy or light immunoglobulin chains are produced in separate cell cultures. Botchan ¶¶ 76-77; McKnight I ¶¶ 92-96; McKnight II ¶ 13; Harris I ¶ 41. Under this plan, Kaplan instructs the person of ordinary skill to produce a bacterial or yeast host cell that expresses a DNA sequence encoding only one immunoglobulin polypeptide. Botchan ¶¶ 76-77; McKnight ¶¶ 93-94; Harris I ¶ 41. Kaplan then directs that person to recover the individually produced heavy and light chain polypeptides from their respective, separate host cells, and combine them under "mildly oxidizing conditions" in a test tube to form the immunoglobulin multimer. Kaplan, p.10, ln. 32; See also McKnight I ¶¶ 92, 95; .

Despite this clear description within Kaplan, and the expert testimony explaining it, the Examiner concludes that

> although Kaplan fails to specifically exemplify the recombinant making of antibodies, Kaplan nevertheless provides a roadmap to one of ordinary skill in the art as to how to do so. Thus, Kaplan ... is additionally relevant to enable co-expressing light and heavy chains in a competent host cell (prokaryotic, eukaryotic or otherwise) to obtain an assembled functional antibody.

Final Action at 39.

Somehow, the Examiner has managed to miss where the expressly stated directions in the Kaplan "roadmap" would have taken a person of ordinary skill in the art in April 1983. As the experts have explained, the Kaplan "roadmap" would have led a person of ordinary skill in the

art down the path defined by the '567 claims of producing only one immunoglobulin polypeptide at a time in a genetically engineered host cell. See, e.g., McKnight I ¶ 96; McKnight II ¶ 13; Botchan ¶ 77.

Contrary to the Examiner's beliefs, Kaplan is entirely silent on the question of producing multiple immunoglobulin polypeptides in one host cell. As the experts explained, based on its express teachings, a person of ordinary skill in the art in early April of 1983 would not have read Kaplan as suggesting in any way that immunoglobulin heavy and light chain genes should be produced in a single transformed host cell.[22] See Harris II ¶¶ 69, 70; Botchan ¶¶ 74-77[23]; McKnight I ¶ 96. Kaplan thus would have led a person of ordinary skill in the art away from the '415 claimed approach of producing an immunoglobulin multimer in April 1983.

II. Moore Also Leads Away from the '415 Claimed Approach of Producing an Immunoglobulin Multimer

The evidence of record also demonstrates that Moore, to the limited extent that it can be considered prior art in this proceeding, also leads the person of ordinary skill away from (rather than toward) the idea of producing immunoglobulins multimers by independently expressing heavy and light chain polypeptides in a single host cell as the '415 claims require.

Moore describes a plan for producing "rFv" binding molecules (i.e., multimeric structures comprised of short variable region polypeptides of heavy and light chain polypeptides). Moore directs the person of skill to produce each of these polypeptides in a separate host cell, then isolate, purify, and combine them in a test tube to form the rFv. See McKnight II ¶ 12; see also Botchan ¶¶ 11-14, 20-27, 32; McKnight I ¶¶ 19-22; Altman ¶¶ 11-12; Scott ¶¶ 8-12. Moore thus describes procedures, like the '567 claims, which require heavy and light chain polypeptides to

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[22] This is particularly relevant to the nonobviousness of claims 17 and 18 directed to transformed host cells comprising at least both the variable domain of the light and heavy chain genes.

[23] As Dr. Botchan explains there is no suggestion in Kaplan to produce a genetic construct that contains both heavy and light chain cDNAs. Botchan ¶¶75-76. This is particularly relevant to the nonobviousness of claims 15 and 16 directed to a vector comprising at least both the variable domain of the light and heavy chain genes.

be produced in separate host cells. See McKnight II ¶¶ 12-13. The Examiner agrees. See Final Action at 5, noting emphasis of Examiner.

Despite this, the Examiner asserts that Moore, when considered with the other cited references, would have provided "further motivation" to make an immunoglobulin multimer by producing heavy and light chains together in the same host cell. Final Action at 15-16. How the Examiner reaches this conclusion is unclear based on his own analysis of Moore, particularly given his conclusion that Moore only teaches production of light and heavy chains in separate host cells. See Final Action at 5-6 (finding Moore is entitled to a § 102(e) effective date for "single host expression of variable light and heavy chain for producing single-chain antibody" only as of "the June 5, 1995 date since the original 06/358,414 specification and claims 1-25 only disclose the separate expression of the heavy and light chain antibody fragment in different host cells . . . ."). Indeed, the Examiner's own finding that Moore does not disclose or suggest production of heavy and light chains in one host cell led him to withdraw the rejections of the '415 claims under §102 and §103 based on Moore in the Final Action. Final Action at 4.

The experts also explained that Moore plainly states that one should produce the light and heavy chain variable region polypeptides in separate host cell cultures, and does not even mention the idea of producing both immunoglobulin polypeptides in a single transformed host cell. Scott ¶¶ 8-12; Altman ¶¶ 10-11; McKnight I ¶ 46; McKnight II ¶ 12. Thus, the experts concluded that Moore, like Kaplan, provides an express direction to the person of ordinary skill in the art to make an immunoglobulin multimer in a test tube using heavy and light chain polypeptides that have been recovered from different host cells. See, e.g., McKnight II ¶ 12 ("What Moore says to do is produce each of the heavy and light chain polypeptides in separate host cells, and then combine them in a test tube to form the rFv.").

F. Dallas Would Have Been Considered Irrelevant to Production and Recovery of Multimeric Eukaryotic Proteins in April 1983

I. The Dallas Method of Making a Whole-Cell E. coli Vaccine Would Not Have Made Producing a Multimeric Immunoglobulin Obvious

Dallas describes techniques for making a whole-cell vaccine by inserting into one E. coli cell genes obtained from another strain of E. coli. Dallas at 3, lines 20-28. The end product of

the Dallas invention is this same E. coli cell, which is administered to a mammal to raise an immune response in that mammal to the antigens expressed on its cell surface. Ibid.; see also id. at 10, lines 5-15; McKnight II ¶ 40. The benefit identified by Dallas for transforming one E. coli cell with genes obtained from another strain is to cause a single cell to have on its cell surface more than one "antigenic determinant." See Dallas at 4, lines 4-18. In other words, Dallas is outlining an alternative strategy for making a multivalent vaccine that, instead of combining different E. coli strains, uses one E. coli cell that looks like multiple E. coli strains to the immune system when it is injected into the mammal. See Dallas at 7, lines 8-20; see also McKnight I ¶ 99; McKnight II ¶ 40; Botchan ¶¶ 79-80.

The E. coli genes used to make the Dallas whole cell vaccine are simple, as are the small monomeric E. coli polypeptides they encode. See Harris II ¶ 74; McKnight I ¶ 100. Dallas explains that these polypeptides are cell surface antigens, which reside in the cell membrane of the E. coli as discrete entities. Dallas at 1, lines 30-34, and at 3, lines 20-28; McKnight II ¶ 40. Indeed, it is necessary to realize the "objects" of the Dallas invention that these bacterial polypeptides (i) not be combined into a multimeric structure, and (ii) not be recovered from the transformed E. coli cell. Dallas at 3, lines 3-16; see also McKnight II ¶ 43; McKnight I ¶ 99; Harris II ¶ 76. If either event occurred, it would defeat the essential purpose identified in Dallas of producing a new E. coli cell that will present distinct antigenic determinants on its cell surface, which the immune system will recognize as being "foreign." See Harris II ¶ 76; McKnight II ¶ 43; Botchan ¶ 79. See, e.g., In re Gordon, 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984) (holding that a modification that would render the prior art "inoperable for its intended purpose" supports non-obviousness.).

These essential features of the Dallas invention are set forth in plain and understandable terms in the Dallas disclosure, and would not have been missed by a person of ordinary skill in the art when reading and assessing the significance of Dallas in April 1983. Nonetheless, the Examiner has reached the conclusion that the disclosure in Dallas would have been considered relevant to the '415 claimed invention by a person of ordinary skill in April 1983. There are several reasons why it is not.

First, the E. coli genes used in Dallas are not "foreign" to the E. coli cells that are transformed with them. Instead, due to the nature of bacteria like E. coli, they are essentially "endogenous" to the E. coli cells that are transformed with them. As Dr. McKnight explained,

> By April 1983, it was known that E. coli cells could easily incorporate and express E. coli genes from other E. coli cells or bacteriophages. The mechanisms that enabled this to happen in E. coli are unique to these types of prokaryotic cells. For example, it was known that bacterial genes often included specific sequences that enabled them to be readily taken up by the bacterial cells.

McKnight II ¶ 41. This would have made the tasks of transforming and achieving expression of these E. coli genes in an E. coli cell a trivial task, even in April 1983. Eukaryotic genes and eukaryotic host cells have no comparable structures that facilitate this essentially "automatic" process of transformation and expression that occurs in bacteria. Eukaryotic genes also have far more complex structures than bacterial genes. For example, unlike prokaryotic genes, eukaryotic genes have non-coding "intervening" sequences (introns) as well as complex regulatory control sequences (promoters/enhancers) relative to prokaryotic genes. See Rice II ¶ 42 and Harris, Genetic Eng. 4:127-185, 131 (1983). The "foreign" DNA sequences encoding eukaryotic polypeptides required by the '415 claims are certainly not comparable to the E. coli genes used in Dallas.

Second, the small cell surface bacterial polypeptides encoded by the E. coli genes used in the Dallas experiments also are not "foreign" to the E. coli cells that are the subject of Dallas. As Dr. McKnight explained, "[i]nstead, they are proteins that normally are destined for the display on the cell surface of the E. coli." McKnight II ¶ 42. In other words, the E. coli cells that are transformed in the Dallas procedures know what to do with these E. coli polypeptides once they are produced within the transformed E. coli cell. By contrast, as Dr. McKnight explained, "when foreign eukaryotic proteins like immunoglobulin polypeptides are produced in a bacterial cell, they usually form inclusion bodies – solid aggregates of the polypeptides." McKnight II ¶ 42.

Third, the expression products of the Dallas experiments are never recovered from the host cell, or used in any other capacity. Instead, they are produced in the cell, and subsequently must reside in the transformed E. coli cells for the Dallas invention to work. Dallas provides no

guidance on genetic engineering strategies designed to produce and recover foreign proteins from recombinant host cells. See Harris II ¶¶ 72, 76; McKnight II ¶¶ 39, 48.

Fourth, in spite of the simplicity of these experiments, Dallas reports unpredictability in their results. These include instability of a bacterial host cell transformed with two different vectors, as well as significantly diminished levels of expression when two bacterial genes were inserted into the bacterial cell. See McKnight II at note 27; Harris II ¶ 77. This unpredictability in the Dallas experiments occurred despite the fact that their structural features and the cellular processes inherent to E. coli cells allow them to be readily assimilated and expressed in the transformed E. coli cells used in the experiments. See McKnight II ¶ 41.

Finally, Dallas is completely silent on any strategy for producing any type of multimeric protein structure, particularly those required by the '415 claims. See McKnight II ¶ 40. Instead, as the experts explained, Dallas would not have shed any light on how to produce a multimeric protein in 1983. See, e.g., McKnight II ¶¶ 43-48.

In view of the vast difference in complexity between the Dallas work and the '415 claimed invention, a person of ordinary skill would not have found use of the Dallas teachings even relevant. See Botchan ¶ 82. As Dr. Botchan explained:

> The PTO apparently believes Dallas has outlined a broadly applicable procedure for coexpressing different proteins in a single host cell. I do not agree with the PTO's use of Dallas, because I believe that a person of ordinary skill in 1983 would not have considered the Dallas application relevant to the problem of making large eukaryotic proteins, such as immunoglobulins, much less to the problem of producing an antibody through coexpression of two complex eukaryotic proteins in one host cell.

Botchan ¶ 78. See also McKnight II ¶¶ 39-47; McKnight I ¶¶ 97-102; Harris II ¶¶ 72-78; Botchan ¶¶ 78-82; Rice II ¶¶ 41-43.[24]

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[24] The observations made by the experts also show that a person of ordinary skill would not have considered the Dallas experimental designs involving use of bacterial genes to be relevant to vectors containing DNA sequences encoding eukaryotic polypeptides, such as those comprising the variable domains of the light and heavy chains of an immunoglobulin. This observation bears particularly on the nonobviousness of claims 15 and 16 concerning recombinant vectors.

Thus, Dallas does not describe or suggest techniques that would be suitable for producing and recovering immunoglobulin heavy and light chains from a single E. coli host cell. Instead, a person of ordinary skill in the art would have viewed Dallas as describing an experiment with a fundamentally different goal – production of a whole cell bacterial vaccine that does not involve recovery of the expression products of the genes that have been inserted into the cell. The Examiner substantially overstates both the technical content of Dallas and its teaching value when viewed in combination with the other references cited in the rejection.

A person of ordinary skill in the art also would have seen no potential advantage in attempting to produce more than one immunoglobulin polypeptide at a time a single bacterial host cell in the manner of the Dallas experiments. McKnight II ¶ 46. Such a person would have been familiar with the many complications of producing eukaryotic polypeptides in bacterial host cells known by April 1983. McKnight II ¶ 47; Harris II ¶ 77. That person also would have known that bacterial cells have none of the specialized capabilities of mammalian lymphocyte cells (the cells that naturally produce antibodies). As Dr. McKnight explained, in view of these factors, a person of ordinary skill:

> would have simply avoided all these problems and uncertainties by producing the heavy and light immunoglobulin chains in separate bacterial host cell cultures. This is what each of the Moore and Kaplan references recommends doing and what the '567 Cabilly patent claims call for.

McKnight II ¶ 48.

In summary, Dallas simply would have provided no impetus for the person of ordinary skill in the art to depart from the path set by the '567 claimed method of producing only one immunoglobulin polypeptide at a time in a host cell. As Dr. McKnight explained:

> All of the references I have discussed above [Axel, Rice, Kaplan, Moore, Ochi, Oi] tell me that if a person of ordinary skill in the art wanted to try to produce an immunoglobulin molecule using recombinant DNA techniques in April 1983, that person would not have tried to do this by producing both immunoglobulin chains in one transformed host cell. The Axel, Rice, Ochi and Oi references make this clear in the context of eukaryotic host cells, and the Kaplan and Moore references explicitly say to produce only one immunoglobulin chain at a time in a single prokaryotic host cell. The experimental results reported in these references would have given a person of ordinary skill no basis to predict or expect that it would be possible to achieve what is required by the '415 patent.

> The Dallas publication would not have changed the clear message I see in these references.

McKnight II ¶¶ 38-39.

II. The Examiner Distorts the Relevance of Dallas with Hindsight

The Examiner asserts, without any evidentiary support, that Dallas provides a specific suggestion to modify the combined teachings of the '567 patent claims, taken in view of Axel, Rice, and Kaplan. Final Action at 14. In particular, the Examiner reads Dallas as teaching "that two different proteins (in addition to a selectable marker) can be expressed in a single cell and such expression may be accomplished by the use of two vectors, each containing DNA encoding one of the proteins, or by use of a single vector that contains DNA encoding each of the proteins." Final Action at 13. See also id. at 39-40, where the Examiner asserts that "Dallas teaches that two different proteins (in addition to a selectable marker) can be expressed in a single host cell and such expression may be accomplished by the use of two vectors, each containing DNA encoding one of the proteins, or by the use of a single vector that contains DNA encoding each of the proteins."

The extensive evidence of record shows that the Examiner has incorrectly portrayed the actual teachings of Dallas and what their significance would have been to a person of ordinary skill in the art in April 1983. Indeed, the fact that the Examiner even relies on Dallas at all reveals that he has improperly "slip[ed] into use of hindsight" and failed "to resist the temptation to read into the prior art the teachings of the invention in issue," in conflict with the Supreme Court's guidance in Graham, 383 U.S. at 36, 148 U.S.P.Q. at 474. See also KSR, 127 S. Ct. at 1731, 82 U.S.P.Q.2d at 1397.

The Examiner clings to his personal views on Dallas despite the reasoned testimony of several experts who explained why a person of ordinary skill in the art would not have found Dallas relevant to production of two complex eukaryotic polypeptides in any type of host cell. See, e.g., Harris II ¶¶ 71-78; Rice II ¶¶ 41-43; Botchan ¶¶ 78, 82, 83; McKnight I ¶¶ 97, 100, 101. This § 1.132 evidence, uncontroverted on this record, firmly establishes that a person of ordinary skill would not have considered successful transformation and expression of simple E. coli genes in an E. coli cell as being comparable in any respect to achieving successful

independent expression of heterologous eukaryotic DNA sequences encoding light and heavy immunoglobulin polypeptides in a single transformed bacterial cell in April 1983. See McKnight II ¶ 41.

For example, Dr. McKnight explains that from an experimental standpoint, a person of ordinary skill would not have viewed the processes described in Dallas involving bacterial genes as presenting technical challenges at all comparable to introducing and expressing foreign DNA sequences encoding eukaryotic polypeptides. As explained above, the incorporation and expression of inserted E. coli genes in E. coli host cells are essentially natural processes that are in no way analogous to the genetic manipulations that would be required to produce a bacterial or other host cell that independently expresses foreign DNA sequences. See McKnight II ¶¶ 41, 42. A person of ordinary skill also would not have expected the transformed E. coli cells to exhibit any problems in producing or processing the corresponding expression products because the encoded polypeptides are essentially "endogenous" to the cells. See id. ¶ 42.

Dr. McKnight also observes that a person of ordinary skill in the art would have perceived no practical advantage – and thus no "motivation" – to using the Dallas experimental system to produce immunoglobulin polypeptides, since any benefits would be more than offset by the additional challenges and complexity of expressing two different immunoglobulin polypeptides in a single bacterial cell. See McKnight II ¶ 46.

Rather than teaching generally that "two different proteins … can be expressed in a single [host] cell," as the Final Action asserts, Dallas actually shows nothing more than that one can transform a bacterial cell with two or more bacterial genes. McKnight II ¶¶ 39-41. This in itself was not a significant experimental achievement in April 1983. See Harris II ¶ 73. A person of ordinary skill in the art in early April 1983 would not have found any relevant insights in Dallas concerning production of two complex eukaryotic proteins in a single transformed bacterial host cell. See McKnight II ¶¶ 42-47; Botchan ¶ 78; Harris II ¶¶ 71-72.[25]

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[25] This is also particularly relevant to the nonobviousness of claims 17 and 18 directed to transformed host cells comprising at least both the variable domain of the light and heavy chain genes.

The Office also found the disclosure of the U.S. counterpart to Dallas to be extremely limited. During examination of the U.S. counterpart to Dallas (eventually issued as U.S. Patent No. 5,137,721, [App. B1800-B1804]), the Office determined that "the disclosure is enabling only for claims limited in accordance with the disclosure at pages 5-11" of the Dallas specification. See Patent Application No. 07/307,223, Paper No. 11, Office Action mailed June 5, 1984 at 3. In other words, consistent with the limited "teaching value" of Dallas at the time, and consistent with the opinions of experts in this proceeding, the Office found that Dallas enabled only its disclosed E. coli host and E. coli protein examples. Dallas eventually conceded this point, accepted these limited claims, and emphasized that "[t]he novelty of the invention is the use in a vaccine of whole cell non-pathogenic E. coli." See Patent Application No. 07/307,223, Paper No. 18, Reply filed February 20, 1987, [App. B1826-1835] at 3.[26]

The Examiner also specifically asserts that Axel would have motivated a person of ordinary skill to use eukaryotic hosts in preference to the prokaryotic hosts used in Dallas. Final Action at 40. Substituting eukaryotic host cells for the prokaryotic cells used in the Dallas experiments as the Examiner suggests would frustrate the primary objective of the Dallas invention (i.e., production of a whole-cell vaccine that retains in it the foreign protein antigens encoded by the bacterial genes used to transform the cell). The Examiner's incorrect assertions that Dallas would have been viewed as being relevant to Axel thus conflicts with the contrary evidence provided by qualified experts, and is nothing more than a hindsight driven, factually incorrect post-hoc analysis.

G. Ochi Demonstrates Unpredictability in a Far Simpler Experiment than What Is Required by the '415 Claims

The Examiner cites Ochi as one of the publications that provide "further motivation" to a person of ordinary skill in the art to modify the '567 claimed invention to arrive at the '415 claimed invention. Final Action at 14. The Examiner asserts that the experiments in Ochi would have led a person of ordinary skill in the art in April 1983 to have reasonable expectation that,

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[26] See also additional correspondence on this issue in the Dallas file wrapper, including Dallas October 28, 1982 Office action (Paper No. 4) [App. B1800-1804] at 4; Dallas June 5, 1984 Office action (Paper No. 11) [App. B1811-1818] at 3-4; Dallas November 17, 1986 Office action (Paper No. 17) [App. B1819-1825] at 3.

following expression of foreign heavy and foreign light immunoglobulin genes in a host cell, one would observe successful assembly of a multimeric immunoglobulin structure. Final Action at 15. As the evidence of record shows, the Examiner is again incorrect.

Like Rice, Ochi describes an experiment where only one foreign (exogenous) light chain gene was used to transfect a hybridoma cell line, and the cell line used was already successfully expressing its endogenous heavy chain genes. See Harris II ¶¶ 80, 81, 83; Rice II ¶¶ 34, 35. Dr. McKnight explained that the experimental design in Ochi was extremely constrained – it involved transformation of a mutant hybridoma cell line with a light chain gene obtained from the properly functioning parental cell line of that mutant. McKnight II ¶¶ 31-32; see also Harris II ¶ 83. As the experts explained, the Ochi experiments were designed to test the limited hypothesis that "one could restore gene expression in a cell line that, due to a random mutation, lost its ability to express the same gene." Harris II ¶ 83, citing Ochi, p. 340.

The experts explained that Ochi would not have suggested to one of ordinary skill in the art that "their transfection and expression results would be broadly extendable to any type of cell line or situation." Id. Instead, the observations contained within Ochi actually would have conveyed the contrary message in April 1983. For example, despite the simplicity and constrained nature of its experimental design, Ochi reports significant unpredictability in restoring expression of what was essentially the mutant cell's endogenous light chain gene. See McKnight II ¶ 31. Ochi also reports that they could not explain why they observed varying levels of expression of the introduced light chain gene, and identified a range of possible factors that might be affecting expression of that one foreign gene. Rice II ¶¶ 35, 36. In particular, Dr. McKnight explained that Ochi reports that 14 cell lines were "successfully transformed" with one foreign light chain gene, but only one of these 14 lines showed production of an antibody at levels comparable to the native parental line. See McKnight II ¶ 32. He also explains that Ochi reports that most of the successfully transformed lines produced little or no light chain protein, and showed no or only trace levels of expression of the light chain gene. See id. at ¶ 33, n.24. Thus, Ochi reports unpredictable results in its experiments, and would not been considered to be "broadly extendable" by a person of ordinary skill in April 1983.

Despite this fact, the Examiner asserts that Ochi would have provided "further motivation" to a person of ordinary skill in the art in April 1983 because, in the Examiner's sole opinion, the work reported in Ochi would have been seen as making predictable the production of a multimeric immunoglobulin structure. See Final Action at 14-15. The Examiner's conclusions rest on two fundamental errors. First, as he did with Rice, the Examiner has improperly, and without any evidentiary basis, based his opinions on a hypothetical lymphocyte experiment that is not described or even vaguely suggested in Ochi. Second, the Examiner has again failed to consider the '415 claimed invention as a whole. In this case, he has based his opinions concerning predictability of achieving only one step of the '415 invention (i.e., assembly of a multimeric immunoglobulin) on results shown in a different experimental context than what is required by the '415 claims (i.e., Ochi's host cell-parental gene combination).

Thus, as he did with Rice, Axel and the other cited references, the Examiner fails to properly consider the extensive expert testimony about Ochi in this record. This evidence explains that the unpredictable experimental results reported within Ochi would have suggested that a person of ordinary skill in the art pursue a more conservative approach in attempting to produce an immunoglobulin multimer (i.e., produce only one polypeptide at a time), rather than a more complicated and untested approach. See McKnight II ¶ 37. When combined with the other cited references reporting unpredictable results about other, similarly constrained experiments, Ochi actually serves to reinforce the beliefs of a person of ordinary skill in the art that the '415 claimed invention could not have been predictably achieved based on the '567 patented invention considered with the information in the cited references.

H. Experimental Work in Frog Oocytes Would Not Have Set Expectations for Recombinant Host Cells

The Examiners cites two papers describing experiments conducted by injecting messenger RNA fractions obtained from normally functioning B-cells into frog eggs (oocytes). The Examiner believes these frog oocyte experiments provide "further motivation to make active antibody with a reasonable expectation of success." Final Action at 14 (emphasis added). The Examiner reached his conclusions about the relevance of Deacon and Valle 1981 to the '415 claimed invention by first concluding that the "the difference between vector DNA and mRNA is not substantive." See Final Action at 15. This is a significant scientific error, which renders his

conclusion of relevance of Deacon and Valle 1981 to the '415 claimed invention scientifically improper and contrary to the substantial evidence of record.

I. The Frog Oocyte Experiments Do Not Foretell Results in DNA Transformed Host Cells

The Deacon and Valle 1981 papers describe experiments conducted in oocyte cells obtained from a species of African clawed frog (Xenopus laevis). Colman ¶5. Both papers employ the same general experimental model. First, the eggs are extracted from the frog. Then, a properly functioning B-cell (i.e., one that produces antibodies), typically a hybridoma cell, is obtained and lysed. McKnight II ¶51. From this cell lysate, all of the messenger RNA in the cell is extracted and crudely purified. Botchan ¶ 91; Colman ¶ 15, 32; McKnight II ¶ 51-52. Once this is done, fractions are produced that correlate roughly to ranges of sizes of mRNA molecules (transcripts). Finally, fractions containing mRNA transcripts having the size of those produced when the B-cell expresses its immunoglobulin genes are obtained and injected directly into the oocyte cell using a micropipette. See Deacon (experimental section); Valle 1981 (experimental).

The Xenopus oocyte experimental system takes advantage of the many unique features of the Xenopus oocyte cell (e.g., its immense size, its "promiscuous" capacity to translate mRNA, its unique tolerance for physical manipulations, and its extended viability). See Colman ¶¶ 21-24. While these unique features made the Xenopus oocyte a very useful experimental tool for studying translation of mRNA, they also severely limited the relevance of the results, particularly as to what might happen in a DNA transformed host cell required by the '415 claimed invention. See Colman ¶¶ 21-22; Harris II ¶ 91. See also Botchan ¶ 87. Instead, the evidence of record establishes that a person of ordinary skill in the art in early April of 1983 would not have equated results obtained in experiments where Xenopus oocytes are microinjected with mRNA, as described in Deacon and Valle 1981, with results one could hope to achieve using genetically transformed host cells. These frog oocyte experiments simply would not have changed the reasonable expectations of a person of ordinary skill in April 1983 about being able to predictably achieve the '415 invention as a whole. See, e.g., McKnight II ¶¶ 51-54; Harris II ¶¶ 91-97; Botchan ¶¶ 86-94; Colman ¶¶ 15, 30, 32, 36.

Dr. Colman explains that a person of ordinary skill in the art in April 1983 would not have found experiments where mRNA fractions are microinjected into Xenopus oocytes relevant to introducing and expressing foreign DNA sequences in a genetically transformed host cell. See, e.g., Colman ¶¶ 21-24; Botchan ¶¶ 86-94; McKnight I ¶¶ 105, 107-108; McKnight II ¶¶ 49-54. He also explains that results obtained in the Xenopus oocyte experimental model would not be seen as being representative of what might occur in host cells transformed with foreign DNA sequences according to the '415 patent. See Colman ¶¶ 24, 25; see also Harris II ¶¶ 90-93; McKnight I ¶¶ 105, 107-108; Botchan ¶¶ 89, 91-94; McKnight II ¶¶ 49-54.

II. The Examiner's View that Differences Between mRNA and DNA are "Not Substantive" is Incorrect

Several experts explained that the Xenopus oocyte experiments use mRNA fractions obtained from naturally occurring B-cells that are successfully producing antibodies. See Colman ¶ 15 ("the oocyte experiments employ messenger RNA (mRNA) which has been extracted from cells specialized for, and which actually are producing, functional immunoglobulin.") See also Colman ¶ 30; Harris II ¶ 95; McKnight I ¶ 105. Dr. Harris explains that "mRNA is itself the product of the expression of genes or an introduced DNA sequence by the transcriptional processes of the cell." See Harris II ¶ 95; see also McKnight I ¶ 107; Botchan ¶ 92. Dr. Colman succinctly explained the significance of this aspect of the oocyte experiments:

> By using products of a successful transcription of the immunoglobulin genes, one can bypass the challenge of constructing an appropriate DNA construct with the necessary control and other regulatory elements to (i) successfully transform a host cell and enable transcription of the exogenous immunoglobulin genes, and (ii) achieve the correct balance of heavy and light chain transcripts so that excess expression of heavy chains does not occur.

Colman ¶ 30. In other words, by using a shortcut (i.e., mRNA fractions isolated from properly functioning mature B-cells) Deacon and Valle 1981 entirely bypass the problems being reported in the other cited references.

For example, Dr. Botchan pointed out that using mRNA fractions from a properly functioning lymphocyte avoids one of the major problems Axel identified as the source of its failed efforts to achieve successful expression of any DNA I sequence and recovery of any "functional" desired polypeptides encoded by a DNA I sequence. See Botchan ¶ 91.

Specifically, Axel reported that its "co-transformed" host cells failed to properly transcribe the introduced DNA I sequence (i.e., it failed to produce "correct" mRNA corresponding to the foreign DNA I sequence). Using mRNA from a host cell that has correctly transcribed its endogenous immunoglobulin genes thus provides no answer and no guidance for resolving this shortcoming reported in Axel. It also bypasses questions a person of ordinary skill in the art would have had in April 1983 on topics such as expressing foreign immunoglobulin genes within a genetically transformed host cell. Botchan ¶¶ 88-89. As Dr. Botchan explains:

> Microinjection experiments in Xenopus oocytes do not result in a cell that replicates the cellular environment of a host cell that is translating an mRNA transcribed from integrated DNA. In the microinjection experiment, a very high local concentration of mRNA is injected into a compartment of the oocyte that is prepared to receive and translate the mRNA. In a cell producing protein after transcription of a gene, a very different pathway and a very different cellular environment is observed.

Botchan ¶ 89.

The experts thus concluded that a person of ordinary skill would not have considered these Xenopus oocyte experiments to be even remotely analogous to expression of foreign DNA sequences encoding foreign immunoglobulin heavy and light chain polypeptides in a DNA-transformed host cell. Colman ¶¶ 33, 35; Botchan ¶¶ 91-92; McKnight I ¶ 105. As such, Deacon and Valle 1981 would not have any provided guidance to a person of ordinary skill in the art about how to achieve independent expression of exogenous DNA sequences encoding heavy and light chain polypeptides, much less a basis for reasonable expectations that immunoglobulin assembly will ensue from any expression of the two foreign DNA sequences encoding light and heavy chain polypeptides in a transformed host cell. See Colman ¶¶ 15, 30.

The Examiner also errs in asserting that a Xenopus oocyte is a "host cell" within the meaning of the '415 patent. Final Action at 41. He finds Deacon and Valle 1981 to be relevant in part because of this erroneous finding. The evidence of record clearly demonstrates that a person of ordinary skill in the art would not have found a microinjected Xenopus oocyte to be a transformed host cell within the meaning of the '415 patent claims. See, e.g., McKnight II ¶ 53; Colman ¶¶ 15, 17-25; McKnight I ¶¶ 105, 107-108; Botchan ¶¶ 85-86, 89-92. For example, as Dr. Colman observed, "[b]ecause an oocyte cannot replicate, it cannot function as a host cell as I

understand the meaning of that term from the '415 patent." Colman ¶ 19. Moreover, a Xenopus oocyte is not transformed with DNA pursuant to the experiments in Valle 1981 and Deacon, and will have no "progeny" that contain "genetic information" related to the mRNA that is injected into the Xenopus oocyte cell. See Colman ¶ 19; Harris II ¶ 92; Botchan ¶¶ 86, 93; McKnight I ¶ 105. The Examiner cites no evidence to counter this understanding, but relies instead on his own reading of a passage from the '415 specification.

The Examiner also mistakenly cites attorney argument made by a European patent agent about Valle et al., Nature, 30:71-74 (1982), [App. B166-169] ("Valle 1982") in a European Patent Office opposition proceeding.[27] See Final Action at 42-45. The evidence of record, particularly the testimony of qualified scientists conveying the opinions of persons of ordinary skill in the art in April 1983, establishes that the scientific aspects of the patent agent's statements referenced in the Final Action were incorrect.[28] See, e.g., McKnight I ¶¶ 106-108; Botchan ¶¶ 90-91; Harris II ¶ 95; Colman ¶ 15; McKnight II ¶ 51. It is also notable that the audience for this statement – the EPO Board conducting the opposition proceeding – did not rely in any manner on this statement in its decision.[29]

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[27] The Office has previously indicated its determination that Valle 1982 is cumulative in its teaching to Deacon. See Office Action dated August 16, 2006 [App. B1481-B1520] at 5.

[28] If this attorney argument were to be considered an admission by one of the Owners rather than attorney argument, the M.P.E.P. would prohibit such use of such an admission in this proceeding, as it was submitted by a third party in an ex parte reexamination proceedings. See M.P.E.P. § 2258(I)(F), subsection 2. (addressing the use of admissions "[a]fter reexamination has been ordered", under the subheading "Reexamination Ordered, Examination on the Merits.") The Final Action relies upon a number of cases to justify its use of this alleged admission, but these cases are inapposite because they do not involve admissions submitted by third parties, but rather admissions made by the patent applicant, himself, as part of the application/specification. See Ex parte Seiko Koko Kabushiki Kaisha, 225 U.S.P.Q. 1260, 1262 (Bd. Pat. App. & Interf. 1984); Ex parte Kimbell, 226 U.S.P.Q. 688, 689-690 (Bd. Pat. App. & Interf. 1985); Ex parte McGaughey, 6 U.S.P.Q.2d 1334, 1339 (Bd. Pat. App. & Interf. 1988); In re Nomiya, 509 F.2d 566, 570, 184 U.S.P.Q. 607, 611 (C.C.P.A. 1975).

[29] The statements made to the EPO were cited in the Request for Reexamination Under 35 U.S.C. § 302 and 37 C.F.R. § 1.510 by Elliot M. Olstein, dated December 23 2005, , [App. B1405-1428],at page 29, and Appendix C.

In light of the substantial differences between the experiments involving microinjection of mRNA into frog oocytes and using DNA-transformed host cells, the experts concluded that Deacon and Valle 1981 would not have established any reasonable expectations of a person of ordinary skill in the art in April 1983 about achieving the '415 patent claims. See McKnight II ¶¶ 49-54; Harris II ¶¶ 96-97; Botchan ¶¶ 92-94; Rice II ¶ 45; Colman ¶ 15.

I. Accolla and Builder Add Nothing to the Examiner's Rationale

Accolla and Builder are cited in the final rejection of claims 1-36. However, the Examiner cites specific teachings in these references only in respect of the limitations of certain dependent claims. See Final Action at 19-20. Neither of these references provides any teaching that addresses the deficiencies of the cited references discussed above concerning transformation of a single host cell with DNA sequences encoding immunoglobulin heavy chain and light chain polypeptides, independent expression in such a host cell of the DNA sequences to produce immunoglobulin polypeptides, or production of a multimeric immunoglobulin structure.

J. The Cited References Refute, Rather than Support, the Examiner's Essential Findings Allegedly Supporting his Conclusion of Obviousness

The substantial evidence of record demonstrates that each of the Examiner's essential factual predicates supporting his legal conclusion of obviousness are incorrect. Instead, as the experts explained, in great detail and with reliance on contemporaneous publications,

- each of the differences that exist between the '415 and '567 claimed inventions would have been considered important to a person of ordinary skill assessing the '415 claimed invention and its fundamentally new way of producing a multimeric immunoglobulin structure in April 1983;
- the prior art existing at the time of the invention did not disclose or suggest all of the elements of the '415 claimed invention, contrary to what the Examiner asserts,
- the prior art, particularly in view of the knowledge held by those working in the field in April 1983, actually directs the person of ordinary skill in the art to take a different path to produce an immunoglobulin molecule (i.e., produce each chain in a separate host cell and form the multimer in a test tube) rather than the path required by the '415 claims, and
- without the teachings in the Cabilly disclosure, the cited references (e.g., showing unpredictability in simpler experiments than what is required by the '415 claimed invention), would not have provided a person of ordinary skill with a reasonable

basis for believing the '415 claimed invention could have been predictably achieved in April 1983.

The Examiner's post-hoc and highly inaccurate characterization of the cited references fails to establish a prima facie showing of obviousness-type double patenting.

(v) Substantial Evidence of Secondary Considerations Supports the Conclusion that the '415 Patent Claims Are Not Obvious, and Must Be Accorded Proper Weight

Among the factors that must be evaluated in considering obviousness-type double patenting are objective indicia of nonobviousness, also referred to as secondary considerations. See M.P.E.P. § 804(II)(B)(1). See also KSR, 127 S. Ct. at 1739, 82 U.S.P.Q.2d at 1395 (directing courts to consider "secondary considerations that would prove instructive" when applying the Graham factors). Secondary considerations "constitute[] independent evidence of nonobviousness," and "may often be the most probative and cogent evidence of nonobviousness in the record." Ortho-McNeil Pharmaceutical, Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1365, 86 U.S.P.Q.2d 1196, 1202 (Fed. Cir. 2008).

Licensing practices showing industry respect/acquiescence and evidence of commercial success are particularly relevant secondary considerations. See WMS Gaming Inc. v. Int'l Game Technology, 184 F.3d 1339, 1360, 51 U.S.P.Q.2d 1385, 1400 (Fed. Cir. 1999); Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957, 43 U.S.P.Q.2d 1294, 1297 (Fed. Cir. 1997); Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1539, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1983). As the Federal Circuit explained in Arkie Lures, successful sales of a patented invention and numerous licenses granted pursuant to the patent "are tributes to ingenuity." 119 F.3d at 957, 43 U.S.P.Q.2d at 1297. There must, of course, be a nexus between the objective evidence of nonobviousness and the claimed invention at issue, as there is in this instance. WMS Gaming Inc., 184 F.3d at 1360, 51 U.S.P.Q.2d at 1400. That nexus is present here.

The record contains compelling evidence of nonobviousness of the '415 patent claims over the '567 patent claims, based on its licensing record and commercial success. As explained in the declaration of Dr. Fintan Walton under 37 C.F.R. § 1.132, the '415 patent claims have been extensively licensed throughout the biotechnology and pharmaceutical industries, and enjoy substantial commercial success. Dr. Walton's analysis of the '415 licensing history and revenue

(i.e., with conservative estimates of '415-specific licensing revenue exceeding $346 million) provides substantial evidence of industry respect for, and acquiescence of, the '415 patent. Walton ¶¶ 25-27, 37-41. This evidence also demonstrates substantial commercial success of the '415 patented invention, and that this success is independent of the success of the '567 patent claims. See id. at ¶¶ 44-46. Both factors provide compelling secondary indicia of non-obviousness of the '415 patent claims, and do so in particular relevance to the '567 patent claims.

The Advisory Action states that this evidence "was considered but deemed insufficient to outweigh the prima facie case of obviousness double patenting already of record." Advisory Action mailed July 19, 2008, [App. B1638-43], at 3. The Advisory Action adopted an erroneous framework, as secondary considerations must be evaluated along with the other facts on which the earlier conclusion of obviousness was reached, not against the conclusion itself. See In re Eli Lilly & Co., 902 F.2d 943, 945, 14 U.S.P.Q.2d 1741, 1743 (Fed. Cir. 1990), citing In re Piasecki, 745 F.2d 1468, 1472, 223 U.S.P.Q. 785, 788 (Fed. Cir. 1984) and In re Rinehart, 531 F.2d 1048, 1052, 189 U.S.P.Q. 143, 147 (C.C.P.A. 1976). That is, the Examiner erred by failing to consider Dr. Walton's declaration in conjunction with the other declarations negating the Examiner's position that the art suggested the '415 patent claims, and by simply considering it for its independent "knockdown" ability. Id. ("An earlier decision [of prima facie obviousness] should not, as it was here, be considered as set in concrete, and applicant's rebuttal evidence be evaluated only on its knockdown ability.").

(vi) The Examiner Either Ignored or Improperly Dismissed the Testimony of Qualified Experts in the § 1.132 Declarations

As the record shows, the Examiner has not interpreted the cited art using the required perspective of a person of ordinary skill in the art in April 1983.[30] He has repeatedly ignored or improperly dismissed the extensive evidence of record demonstrating what the understanding of those with the proper perspective would have been in April 1983, and substituted his own unsupported views or, in one instance, the personal opinions of a person (Dr. Baltimore) that clearly was not one of ordinary skill in the art in April 1983.

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[30] The expert declarants agreed that a person of ordinary skill in the art would be an individual with a Ph.D. in molecular biology or a comparable degree, and about two years of post-doctoral or laboratory experience. See, e.g., Harris II ¶ 5; Rice II ¶ 8; Colman ¶ 7.

As noted above, the record of § 1.132 evidence in this reexamination is substantial. Each of the experts who presented testimony on behalf of Owners in this proceeding (i) had personal experience working in the field of the invention in April 1983, (ii) had the credentials of or worked with persons of ordinary skill in the art at that time, and (iii) in several instances co-authored one or more of the cited references or had published relevant papers contemporaneous to the filing date of the '415 patent. Each of these experts also provided well-reasoned and supported explanations of what the cited references actually described and would have taught a person of ordinary skill in the art in April 1983, and pointed out numerous scientific errors made by the Examiner.

The Examiner committed serious legal error by repeatedly substituting his own interpretations of the cited references for the well-reasoned opinions of qualified experts. See In re Zeidler, 682 F.2d 961, 967, 215 U.S.P.Q. 490, 494 (C.C.P.A. 1982) (Board committed reversible error in "substitut[ing] its judgment for that of an established expert in the art" to assess obviousness); In re Katzschmann, 347 F.2d 620, 622, 146 U.S.P.Q. 66, 68 (C.C.P.A. 1965) ("We do not think it was the intent of section 103 that either the examiner, the board or this court should substitute their own speculations for the factual knowledge of those skilled in the art. "); In re Fay, 347 F.2d 597, 603, 146 U.S.P.Q. 47, 51 (C.C.P.A. 1965); M.P.E.P. § 716.01 et seq. Relevant § 1.132 declaration evidence from a qualified expert is entitled to particular deference by the Office. See M.P.E.P. § 716.01(c); Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143, 227 U.S.P.Q. 543, 551(Fed. Cir. 1985) ("A retrospective view of the invention is best gleaned from those who were there at the time."); In re McKenna, 203 F.2d 717, 720, 97 U.S.P.Q. 348, 350 (C.C.P.A. 1953) ("affidavits are clearly one of the few practical methods of presenting a factual record sufficient to form a basis for proper application of the 'history of the art test' in this type of ex parte proceeding." (internal citations omitted)).

The Examiner also erred by repeatedly failing to consider all of the testimony offered and specifically address substantial portions of that testimony in his actions. See, e.g., M.P.E.P. § 716.01 ("All entered affidavits, declarations, and other evidence traversing rejections are acknowledged and commented upon by the examiner in the next succeeding action. The extent of the commentary depends on the action taken by the examiner . . . Where the evidence is

insufficient to overcome the rejection, the examiner must specifically explain why the evidence is insufficient.").

By demonstrating with substantial evidence that the Examiner's essential scientific conclusions about the '567 claims and the cited references were wrong, Owners have shown that the rejections built on these factual errors are improper. An erroneous interpretation of a reference teaching skews the foundation on which the obviousness double patenting rejection rests. See, e.g., In re Rouffet, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453, 1455 (Fed. Cir. 1998) ("[A]n applicant may specifically challenge an obviousness rejection by showing that . . . the Board based its obviousness determination on incorrect factual predicates.").

The Examiner's general approach in responding to the declaration evidence in this reexamination has been either to ignore it while substituting his own opinions, or to dismiss it as not addressing the "combined teachings" of the cited references and the '567 claims (see, e.g., Final Action at 28). Both approaches are clearly improper, are based on often incorrect readings of the declarations, and show that the Examiner has not given the declarations the meaningful consideration and deference that he is required to by prevailing law and Office practices. Cf. In re Sullivan, 498 F.3d 1345, 1352-53, 84 U.S.P.Q.2d 1034, 1040 (Fed. Cir. 2007) (remanding with instructions that Board "must give the declarations [previously dismissed as not bearing on the obviousness issue] meaningful consideration before arriving at its conclusion [that the claimed compounds which were not previously known in the art were nonetheless obvious]"). As explained above, each of the § 1.132 declarants clearly explained that he had, in fact, considered each reference both as to its individual teachings, and to what it might have conveyed in conjunction with the teachings of the other cited references. See, e.g., McKnight II ¶¶ 4-16, 37, 48, 49-50, 55; McKnight I ¶¶ 3, 64, 78, 91, 102; Botchan ¶¶ 4, 104; Harris II ¶¶ 6, 78, 86; Rice II ¶¶ 38-45; Harris I ¶ 5.

(vii) The Board Should Give Weight to the Numerous Past PTO Determinations, Including Those of the Board, Finding the Approach Required by the '415 Claims Patentably Distinct from that Required by the '567 Claims

Before the present reexamination, the Office consistently found claims presented in the format of the '415 claims (i.e., requiring production of two desired polypeptides in one host cell)

to define a patentably distinct invention relative to claims presented in the form of the '567 claims (i.e., requiring production of only a single immunoglobulin polypeptide in a host cell). See, e.g., the '419 application, Office action mailed September 7, 1990 at 2, Exhibit I of Declaration of Wendy M. Lee, [App. B1243-1365], ("Lee"), Interview Summary dated October 4, 2001, Lee, Exhibit O. The first instance of this was when the Office issued separate patents with claims corresponding to the '567 and '415 claims to different parties on the same day (i.e., March 29, 1988). Then, during the examination of the '415 claims, the Office found claims requiring production of heavy and light immunoglobulin chains to be patentably distinct from claims requiring production of only one chain. See '419 application, Office action mailed September 7, 1990; Lee, Exhibit I. And, following the conclusion of the interference involving the '415 patent (i.e., Interference No. 102,572), the Office specifically concluded that the '415 claims did not raise obviousness-type double patenting issues relative to the '567 claims. See '419 application, Interview Summary dated October 4, 2001; Lee ¶¶ 20-23.

The Board also shared this perspective. At the start of the '572 Interference, the Board designated only those Cabilly claims requiring production of heavy and light chains in one host cell as corresponding to the Count of '572 Interference (which correlates to claim 1 of the '415 patent). See Lee, Exhibits L; M, and N; the '419 application, July 25, 2001 Order. During the '572 Interference, the Board declined to exercise its discretion to involve the '567 patent based on the '415 claims. And, in its Order implementing the judgment of the district court in the action under 35 U.S.C. § 146 arising out of the '572 Interference, the Board confirmed its finding of fact that only claims requiring production of heavy and light chains in one host cell corresponded to the count.

This record contradicts the views of the Examiner in this case, formed some 25 years after the effective filing date of the '415 application, that there is no patentable distinction between the conceptually different approaches reflected in the '567 and '415 claimed inventions. As the extensive record in this case shows, there is no scientific basis for the Examiner's new position on the lack of patentable distinctness between the '415 and '567 claimed inventions.

(viii) The Examiner Erred as a Matter of Law in Repeatedly Treating the '567 Patent Disclosure as Prior Art

The Examiner erred as a matter of law by using the "teachings" of the common patent specification and the '567 claims to find motivation, guidance, or a suggestion to modify the '567 claims to arrive at the '415 patent claims. When comparing the claims for obviousness-type double patenting purposes, it is well-established that "the [earlier] patent disclosure may not be used as prior art." In re Vogel, 422 F.2d 438, 441, 164 U.S.P.Q. 619, 622 (C.C.P.A. 1970); see also General Foods Corp., 972 F.2d at 1281, 23 U.S.P.Q.2d at 1846; In re Kaplan, 789 F.2d 1574, 1579, 229 U.S.P.Q. 678, 682 (Fed. Cir. 1986); Chisum, Patents, § 9.03[1][a] (2005).

The Examiner's analysis in the Final Rejection directly conflicts with this core principle of obviousness-type double patenting analysis, and makes the fundamental error of using the '567 patent claims and specification as if they were prior art. In particular, in the Final Action, the Examiner states:

- "it is appropriate to construe the reference *Cabilly 1* patent claims to suggest production of chimeric immunoglobulins using recombinant technology, and vectors and host cells for doing so." (Final Action at 12) (underlining added)
- "instant claim 22 represents an obvious variant of the reference *Cabilly 1* patented invention in light of the reference *Cabilly 1* patented claimed teaching and the art-recognized motivation" (Final Action at 20) (underlining added)
- "the *Cabilly 1* patent claims teach the recombinant method of making light and heavy chains which would motivate one of ordinary skill in the art to make an antibody or antibody fragment" (Final Action at 23) (underlining added)
- "it is the *Cabilly 1* patented invention . . . that provides the teaching or suggestion of assembling an antibody" (Final Action at 23) (underlining added)
- "the *Cabilly 1* patented claims *suggest* antibody assembly" (Final Action at 24) (underlining added)
- "In light of the *Cabilly 1* patent's claimed teaching . . . it is reasonable to one of ordinary skill in the art to interpret the *Cabilly 1* patented invention as suggesting the use of the *Cabilly 1* claimed immunoglobulin chains for assembly into antibodies" (Final Action at 25) (underlining added)

When the Examiner uses the specifications or the claims of the '567 patent to find suggestions, teachings, and motivations – as clearly evidenced in the quoted passages above – he is improperly using the disclosure of those claims and specifications as prior art teachings. This approach violates the fundamental principle that the only use of the earlier patent is to consider

what invention is being claimed, not what the claims or specifications might teach or suggest to one of ordinary skill in the art, or how they might motivate that person. As the Federal Circuit explained in General Foods Corp., "[the] comparison can be made only with what invention is claimed in the earlier patent, paying careful attention to the rules of claim interpretation to determine what invention a claim defines and not looking to the claim for anything that happens to be mentioned in it as though it were a prior art reference." 972 F.2d at 1280, 23 U.S.P.Q.2d at 1845. See also In re Aldrich, 398 F.2d 855, 859, 158 U.S.P.Q. 311, 314 (C.C.P.A. 1968) ("double patenting rejections cannot be based on . . . the disclosures of the patents whose claims are relied on to demonstrate double patenting or on the 'disclosures' of their claims.") (emphases added); In re Sarett, 327 F.2d 1005, 1013, 140 U.S.P.Q. 474, 481 (C.C.P.A. 1964)(explaining that, in evaluating obviousness-type double patenting, "[w]e are not here concerned with what one skilled in the art would be aware from reading the claims but with what inventions the claims define.").

The record also shows that there was no need for the Examiner to consult the common disclosure of the '415 and '567 patents, and that he, in fact, did not use the specification to clarify what the terms of the '567 or '415 patent claims defined. See, e.g., Final Action at 11 (recognizing meaning of the phrase chimeric immunoglobulin heavy or light chain and referring to col. 6, lines 38-59 of the '567 patent.) Two different experts explained that the language used in the '415 and '567 claims was clear and would have been readily understandable to a person of ordinary skill in the art in April 1983. Harris I ¶¶ 11-14; McKnight I ¶¶ 18, 26, 32; McKnight II ¶¶ 14-16. In other words, because one of skill could have readily understood what both of the patents defined, there was no need for the Examiner to delve into the common patent disclosure to "interpret" these two claimed inventions.

The Examiner attempts to justify his misuse of the teachings of the claims and specifications of the '567 patent by distinguishing the facts of General Foods Corp. from the facts at issue in this reexamination (see Final Action at 26). By doing so, he confirms that he is overlooking the fundamental error of law he makes in using the '567 patent as prior art. General Foods is just one of many cases that has been cited for the fundamental proposition that an evaluation of obviousness-type double patenting cannot consider the first patent as prior art, from which teachings, suggestions, and motivations could be derived. Whether or not the precise facts

of each of those cases can be distinguished from the present case is irrelevant. See, e.g., In re Aldrich, 398 F.2d 855, 859, 158 U.S.P.Q. 311, 314 (C.C.P.A. 1968). ("patent claims are looked to only to see what has been patented, the subject matter which has been protected, not for something one may find to be disclosed by reading them.") Consequently, the Final Action's analysis directly conflicts with a core principle of obviousness-type double patenting analysis.

* * *

Conclusion

For the reasons set forth above, appellant requests that the Board reverse the rejections of claims 1-36.

Respectfully submitted,

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